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WIDE FIELD ROENTGEN THERAPY

WITH REPORT ON CLINICAL INVESTIGATIONS, 1920–1938*

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THERE were several reasons why I chose "Wide Field Roentgen Therapy" as my subject when invited to deliver the Mackenzie-Davidson Lecture at the Annual Congress of the British Institute of Radiology. In the first place the method had been under constant investigation for nearly twenty years and had always been to me a subject of very great interest. Secondly, I consider that it will be in the realm of radiotherapeutics that the greatest advances will be made in the future. Finally, I came to the conclusion that the time was ripe and the occasion appropriate for me to render an account of investigations that were commenced at the London Hospital in 1921 when I was Director of the Radiological Department.

Originally the object of the investigation was to determine whether wide field roentgen therapy could influence, that is prevent, the formation of secondary deposits in malignant disease especially in carcinoma mammae. It is only in the last eight years that it has become evident that this method of roentgen therapy has a much wider scope when applied to the less spectacular benign conditions.

I realized, as anyone with a wide experience of cancer in general and of carcinoma mammae in particular, must realize only too well, that it is rare for the primary growth to destroy the host. The fact that it is the metastases that do all the killing must be faced. From the earliest history of medicine it has always been the formation of secondary deposits that has rendered abortive the various methods devised from time to time for the destruction of the primary growth, whether this be through the agency of hot irons, surgery, roentgen rays or radium, etc. For this reason I have always maintained that even if total destruction of the primary growth were possible in 100 per cent of cases the effect on the cancer problem would probably be negligible; consequently whether it be roentgen rays produced at one million volts or radium in bulk, that is applied *locally* for destruction of the primary growth, a cure cannot reasonably be expected.

Until it is generally appreciated also that so-called deep roentgen therapy is not the *only* method of roentgen application and that cancer is not the *only* condition

* Abstract of the Mackenzie-Davidson Memorial Lecture, delivered at the Annual Congress of the British Institute of Radiology, December, 1937.

that can be benefited by roentgen rays but little progress in radiotherapeutics can be hoped for. The radiological departments of all hospitals are at present designed primarily for the treatment of cancer by the "deep roentgen-ray" method, but it is no use hiding the fact any longer that in this disease the ultimate results, from the curative point of view, are disappointing, although the palliative effects may often be spectacular.

In any case it is surely wrong that the energies of a radiological department should be entirely devoted to the treatment of an interesting but rare disease like cancer, to the exclusion of the less spectacular but more prevalent benign conditions which are known to benefit from roentgen irradiation.

The problem therefore in 1920 was to find some method that had a reasonable chance of preventing and destroying metastases. This vital problem has yet to be solved.

Since the beginning of radiotherapy the application of roentgen rays has always been to a *limited* area, and consequently the biological effect has been limited to this area. Obviously, therefore, this restricted application of roentgen rays cannot be expected to have any influence whatever on preventing the formation of metastases or of destroying secondary deposits which more than likely are scattered throughout the body long before they can be detected clinically. The localized irradiation of the "gland areas" must be equally ineffective. Obviously, therefore, if the power of destroying malignant cells within a localized area was to be extended to the destruction of these stray or wandering malignant cells, the whole body would have to be submitted to irradiation. The question would then arise whether the dose necessary to accomplish this destruction might not at the same time destroy the host. A certain amount of research work that had some bearing on this problem had been carried out during this period (1921).

The conclusions were as follows:

(a) A large dose of roentgen rays was found to be detrimental to health and eventually caused death of the animal —while there was an *increased susceptibility* to tumor growth.
(b) Smaller doses, while detrimental to health, did not endanger life.
(c) Still smaller doses not only improved health but *reduced susceptibility to tumor growth.*[1,2,3,4,5,6]

The whole animal was exposed to irradiation. The last of these findings (c) formed the foundation of wide field roentgen therapy.

It must be clearly understood that there is nothing antagonistic between the intensive local application of roentgen rays—namely, deep roentgen therapy—and wide field roentgen therapy any more than there is between surgery and medicine. Each is used for a specific purpose. Deep roentgen therapy which produces a direct local destructive effect might be called *surgical radiotherapy;* wide field roentgen therapy, on the other hand, as will be shown later, results in an indirect or constitutional effect and for this reason might be termed *medical radiotherapy*. In cancer both methods are probably necessary, one to destroy the primary growth, the other to prevent the formation of metastases. I purposely refrained from publishing the results of this prophylactic method, although at the London Hospital a large number of cases had been treated over a number of years. The fact that the majority of patients treated belonged to the roving population of the East End of London made it possible to follow up only about 1 per cent of cases over a period long enough to estimate results. I have no hesitation, however, in saying, even in the absence of statistics, that wide field roentgen therapy undoubtedly seems to possess, in a certain percentage of cases, the power of reducing the possibility of the formation of secondary deposits. At any rate there is sufficient evidence to justify some cancer research body continuing this investigation into prophylaxis. This new method of applica-

tion certainly opens up new lines of therapy worth investigating on a large scale.

HISTORY

Thanks to the generosity of Mr. Serena, at that time a member of the House Committee at the London Hospital (1921), it became possible to install a specially designed apparatus for this investigation.

The early machine consisted of two roentgen-ray tubes, one in front and the other behind the patient, activated separately but running simultaneously. The tubes were so arranged that at 12 inches the radiation field included the whole trunk, back and front (Fig. 1). The result-

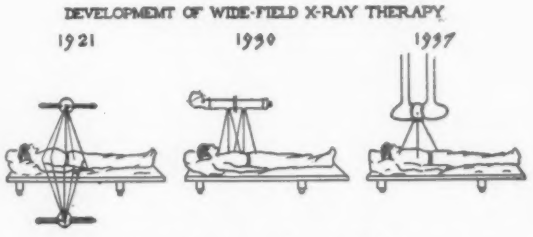

Fig. 1. Development of wide field roentgen therapy.

ing flooding of the tissues, using roentgen rays of long–medium wave length (0.095 Å) made it essential to ascertain whether the patient might not be detrimentally affected and whether he would survive the treatment.

It was about this time that detrimental blood changes, usually a leukopenia, were being reported as occurring among those working with roentgen rays or radium. It was with some trepidation, therefore, that the first cases were submitted to this new method of roentgen application. No record could be found of this method having been tried previously. Several illustrations were, however, found in an old German book on radiology (Fig. 2), suggesting this idea, but the text made it clear that for technical reasons it was never carried out. If it had been developed, I am sure that radiotherapeutics would by now be in a much more advanced state.

The first 50 cases treated by this method were closely watched and a careful record of the blood was kept during the first year. Curiously enough, the ultimate report of the pathologist on these cases was essentially favorable; a general improve-

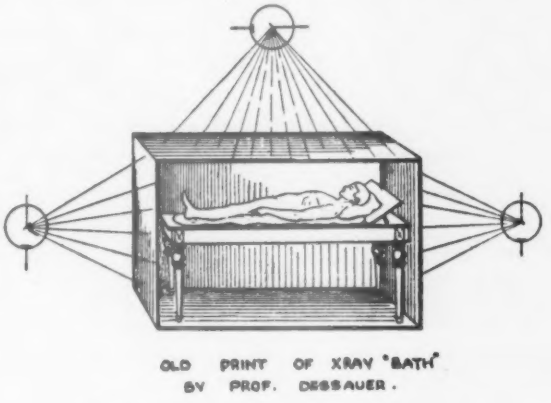

Fig. 2. Old print of roentgen-ray "bath" by Prof. Dessauer.

ment in health and in the blood picture was a constant feature.

This at least meant that no harm was being done, but it was not till some ten years later that the real significance of these findings became recognized.

Wide field roentgen therapy now became established at the London Hospital as a routine in all cases of malignant disease, being used *in conjunction* with any local application (deep roentgen therapy) to the primary growth considered necessary.

These investigations were continued up to the time of my retirement from the London Hospital in 1930, after twenty-two years as Director of the Radiological Department. Thanks to the facilities granted by the Charterhouse Rheumatism Clinic, it has been possible to continue the work, but only in relation to benign and rheumatic conditions, it being realized that, owing to the want of facilities, the cancer problem had for the time being to be shelved, hoping that later some cancer research body might carry on the investigations.

Early in these clinical investigations I realized that further advance in this method of roentgen-ray application was

not to be expected until some tangible test could be found that would register the constitutional change or effect now so clearly demonstrated by the clinical results.

Owing to the practical difficulties, efforts to obtain this evidence from the examination of urine, feces, blood and saliva, etc., at periods before, during and after irradiation proved abortive. The effect on the sedimentation test, however, was found of some value, but unreliable. It was the preliminary work of Bendien that made the introduction of the differential sedimentation test possible. When Dr. Coke, of the Charterhouse Clinic, suggested five years ago (1933) that the method might supply the information I was wanting, I must say that, owing to the complexity and delicacy of the technique, I was very sceptical of its practical value; nevertheless, it was decided to test it out in this research. This test, a serological sedimentation,[7] has now been carried out in a large number of cases treated by wide field roentgen therapy and has enabled this method of treatment to be developed along more scientific and less empirical lines. I have come to compare its use with that of registration of the body temperature. Its actual value lies in the fact that it seems to supply information as to (1) severity of the infection; (2) degree of toxicity; (3) amount of resistance, and this with a considerable degree of accuracy. It also, as will be described later, gives information that is of some assistance in regulating dosage. With wide field roentgen therapy there is a "saturation" point that can be recognized. Dr. Coke states that the differential sedimentation test has shown:

a) that serological changes can be observed as the result of exposure of X radiation, given by the wide field radiation method in comparatively small doses.
b) That having apprehended the nature of such change, the test has been applied as a means of controlling dosage and overdosage that is over-saturation.

The investigation so far indicates that to reach the optimum effect, the patient should be kept as near as possible to the saturation point, over- or under-saturation being avoided. All the skill of a physician is therefore required to estimate the effect of each treatment. Those using deep roentgen therapy will hardly appreciate that the difference between saturation and oversaturation may in some instances be only a matter of 10 r when using wide field roentgen therapy.

Whether the differential sedimentation test will ever become generally established, I do not know; however, these investigations have clearly demonstrated that it possesses a definite value in this method of roentgen treatment and in difficult cases I would not like to be without it, but it should be realized that its use is not essential to the treatment and that good results can be attained if careful attention is paid to the effect of each individual treatment. From the point of view of these investigations, therefore, we have in the differential sedimentation test a means of registering an effect of wide field irradiation on the organism as a whole. This fact has accounted for the advance in technique in recent years.

Let us now consider the fundamental differences between deep and wide field roentgen therapy. It may be said at once that the only thing in common is the use of the same agent. *Deep therapy* means the use of roentgen rays of very short wave length; thick filters; small radiation field; large doses. The effect is of a destructive nature. The radiation beam is locally applied to some objective sign of disease, such as a tumor, enlarged glands, etc. If the mass so treated disappears, the result is considered satisfactory, ignoring the fact that this mass may be but the manifestation of a constitutional condition. A mass of glands in a case of Hodgkin's disease is an example. Such a mass may rapidly disappear under the influence of roentgen rays, but the effect on the disease as a whole is negligible—other glands will eventually develop throughout the body. The

condition, stamina, age, etc., of the patient does not suggest any adjustment of dose. If he does not survive the treatment, the fault lies with the patient and not with the radiologist! The motto of deep therapy may be said to be "the larger the dose, the better the result." One is rather inclined to think that under these circumstances the patient comes to be looked upon as "something" attached to a tumor! This method of roentgen-ray application may, I think, be described as *surgical* radiotherapy, and undoubtedly has its dangers and the reaction unfortunately often lowers resistance beyond recovery in the case of an enfeebled patient.

It may be thought that the only feature of this new method of radiotherapy lies in the fact that the rays are applied to a large, instead of a local, body area. This is wrong. The whole principle is different, requiring an entirely new outlook and a readjustment of ideas.

Wide field roentgen therapy entails the use of roentgen rays of medium wave length, light filters, large radiation field (the whole trunk), optimum distance and small doses (comparative). The effect, moreover, is not local but generalized or constitutional. Briefly, one treats the disease through the patient; the patient, in other words, receives all the attention and not the outward manifestation of the disease. These investigations go to show that in some complex way the patient's resistance can be raised, he is thus able to establish an ascendency over whatever pathological condition he may be suffering from, and if the response is satisfactory, the patient will be in a position to cure himself, irrespective of the disease. In other words, if the findings of these investigations are confirmed, then the necessity for treating each disease as a separate entity will cease—a somewhat revolutionary outlook.

It must be realized that it is natural to be well and unnatural to be ill, and that illness or ill health is nothing more than evidence of a breakdown in this resistance to disease. Nature is always striving to keep us fit, in the same way that she readily repairs any damage, such as fractured bones, wounds, etc., but she cannot have a separate defense against every disease. Our conception of disease is arbitrary and therefore the names of diseases mean nothing to her. She cannot, for instance, have a special defense for typhoid and another for pneumonia. Her methods of defense must therefore be of the simplest kind. If means could be found of keeping this defensive power up to maximum and of restoring it when for some reason or other it has dropped below normal—that is, a lowering of resistance—an incalculable blessing would be conveyed on mankind. There is fortunately something described by Hernaman-Johnson as "that innate tendency of the body to swing back to the rhythm of health—vis mediacatrix naturae."

It is not improbable that an individual who is born with a high resistance and retains this during life, is the one that reaches a ripe old age.

I have deliberately allowed myself to indulge in what some might call fantasy, with the object of accentuating the fundamental differences between the two methods of roentgen therapy. The principles and objects are so entirely different. I am inclined, therefore, to describe the wide field roentgen application as *medical* roentgen therapy. In contrast to the surgical, or deep, roentgen therapy, it is the smaller rather than the larger dose that gives the best results. It might be said that with deep roentgen therapy it is the tumor that is treated and with wide field roentgen therapy it is the patient. The introduction of short wave roentgen therapy, with the additional influence of physicists, has led the radiologist to substitute physics for biology; thus he has become more of a technician and less of a physician, a state of affairs that unfortunately cannot lead to any real advance.

There has always been that tendency to treat the objective sign or signs of disease rather than the disease itself. If a patient

has a lump or a pain and this objective sign disappears with treatment, it is often erroneously concluded that he has reaped some real benefit from the treatment, until the objective signs return in some other part of his body, when it is realized that he is suffering from some constitutional condition, the primary cause of the objective signs.

In the course of these investigations, this fact has always had to be kept in view and additional evidence of improvement has had therefore to be looked for in directions such as an improvement in the blood picture, sedimentation rate, increase in weight, improvement in appearance of the patient, texture of the skin and, above all, the patient being conscious of a feeling of "well-being."

The trial of this method in a large number of cases, embracing many pathological groups, has definitely shown that no two patients respond exactly alike—that the response is greater in the young patient—that there is no danger or possibility of damage in the application of this method, provided the principles are understood and the technical details followed.

THEORY OF ACTION

This research work has made it quite clear, therefore, from clinical results so far obtained that the whole "makeup" of the patient or individual can be influenced by wide field roentgen therapy. How does this come about? What evidence is there to support this contention? What is the evidence that resistance to disease can be raised by this method of roentgen-ray application? Will it ever become possible to register this essential resistance and will means ever be found of keeping it up to a maximum? All pertinent questions. It is humiliating to think that the medical profession can do so little to prevent such complaints as the common cold or influenza. In fact, doctors are unable to show their real worth until it comes to diagnosis or treatment. We want specialists of health as well as of disease. The evidence so far obtained strongly supports the idea that this power of resistance to disease is in some complex manner bound up with the uniform functioning of the ductless or secretory gland system as a unit, an imbalance of which may mean a depression of this resistance automatically followed by the risk of disease or ill-health. My contention, which of course requires much research before it can become established, is that wide field roentgen therapy can restore this endocrine balance. The sensitivity of glandular tissue to roentgen rays in diseases of the thyroid, spleen, etc., is already well established, but the possibility of influencing the ductless gland system as a unit with the possibility of preventing disease has not as yet been considered.

Hirsch (1925) points out in his book "The Principles and Practice of Roentgen Therapy" when dealing with this subject of the effect of roentgen rays on secretory gland tissue, "that with proper *small* doses a stimulation of the secretory function is produced.

"With proper *moderate* doses inhibitory effects with *restitution to normal* of the secretory function may be produced.

"With *large* doses the effects of degeneration and death of the particular tissue may be produced.

"The effect of X-rays on the function of a secreting tissue might therefore be expressed as follows: Destructive dose 100%, inhibitive dose 75%–50%; stimulative dose 35–25%."

Of course I do not know on what authority this work is based but these investigations tend to confirm the findings. At any rate, there is here a vast field for the research worker.

It has been suggested that the preservation of a high resistance should prevent or at any rate reduce the possibility of disease but to prove this will require considerable investigation.

The method has been tried out in various pathological conditions. Working on the assumption, rightly or wrongly, that the therapeutic effect of wide field roentgen

therapy is indirect or constitutional, resulting in a raising of resistance, it soon became evident that irrespective of the pathological group to which the case belonged, if a general response to irradiation could be registered, then the patient got well. Thus one found the clinical results, for example, in spondylitis adolescens were equally as good as those obtained in certain types of asthma, Hodgkin's disease, blood diseases, etc., all belonging to different groups. Of course, the response varies in different individuals, but in most cases this can be accounted for by the stage of the disease, debility and age of the patient, rather than by the actual nature of the disease.

Eventually I was forced to the conclusion that the clinical results were dependent on the response that could be obtained in the patient rather than any effect directly on the disease—meaning that the patient rather than the disease was being treated. At first sight this conclusion appears unreasonable, especially to those engaged in deep roentgen therapy where it is customary for the tumor rather than the patient to receive all the attention. This outlook is not so revolutionary as it appears. Our methods of treating disease are really so limited that in most cases all we can do is to place the patient under conditions that will encourage his recovery, treat his symptoms, and let nature do the rest. Thus medical advice, to go on a cruise, to take a tonic or to have a change at Brighton, are only different methods of treating the patient. Consequently, the time may come when diagnosis will be of minor rather than of major importance, knowing that if a patient feels ill and his resistance by any means can be restored rapidly, his recovery is assured even in the absence of a diagnosis. Of course, this may be considered to be a flight of imagination, but at any rate it helps to accentuate the large gap that exists between the objects of deep and wide field roentgen therapy.

Let us sum up the evidence so far collected during these investigations in support of the contention that the effect of wide field roentgen therapy is of a constitutional character. It is hardly necessary at this stage to stress the importance of this

(a) improvement in the blood picture,
(b) the restoration of the blood sedimentation rate to normal,
(c) the influence on the serum as demonstrated by the differential sedimentation test,
(d) character of the post-irradiation phenomena,
(e) effect on general metabolism,
  (1) increase or decrease in weight,
  (2) feeling of well-being,
  (3) an increase in mental alertness,
  (4) increase in physical fitness,
  (5) improvement in skin texture.

The effect on the blood is possibly the most significant. The registration of the influence on resistance of this form of irradiation as demonstrated by the differential sedimentation test is of special interest and work is to be continued along these lines.

It follows theoretically that if the resistance is raised to all diseases, it should be possible in certain conditions to get the patient well from several pathological lesions at the same time. This has actually happened in several cases. Thus an antrum full of pus cleared up while treating a patient by wide field roentgen therapy for an active spondylitis. Another patient undergoing this treatment for an inoperable sarcoma in the abdomen was cured of his asthma and was alive and well three years later. Migraine and asthma have also been influenced simultaneously. Other cases could be quoted.

TECHNIQUE

Several workers have made use of teleradiotherapy, the distance of the tube to the patient varying from 6 to 24 ft. This, of course, results in a large radiation field, but as I have pointed out the use of a large field alone does not constitute wide field roentgen therapy any more than the use of a small field constitutes deep roentgen therapy.

Heublein[8] describes the arrangement of

a ward where the roentgen-ray tube, running automatically day and night, irradiated 5 patients at once over a period of seven days—twenty hours a day—in some cases even up to thirteen days! A canary placed in the primary beam succumbed after receiving 7 erythema doses! He reports some degree of general stimulation of the metabolism of the patients, but arrived at no conclusion.

A glance through the literature on the use of large radiation fields makes it clear that:

(a) Roentgen rays of short wave length have invariably been used.
(b) The rays have been passed through a copper filter, creating a homogeneous primary beam.
(c) The distance of the tube to the patient has never been less than 6 feet.
(d) The effect has been direct. Even under these conditions favorable results have occasionally been reported.

The essentials of wide field roentgen therapy as used in these investigations may be summed up for comparison, as follows:

(a) The use of roentgen rays of long–medium wave length.
(b) The use of light aluminum filters.
(c) A heterogeneous primary beam.
(d) A large radiation field—the whole trunk.
(e) Optimum distance—a maximum of 20 inches—tube to patient.
(f) The recognition of a saturation or tolerance dose.

(a) *Wave Length.* Most of the recent investigations have been carried out with a wave length obtained at 130–140 kv. The new wide-angle roentgen tube which has been installed at the new Charterhouse Rheumatism Clinic where this work is to be continued will run at a constant rating of 100 kv. The object of this new roentgen tube will be described later.

It must be clearly understood that the choice of wave length is dependent on obtaining the maximum *body absorption.* Penetration must be adjusted accordingly. I do not propose to become involved in physics. But the choice of wave length and the number of roentgens administered when using this method must be entirely dependent on the effect produced on the individual, similar to the administration of drugs.

(b) *Filters.* The primary use of a filter is to absorb those rays that are not required. With the use of the longer wave lengths, it is the skin that has to be protected. Three millimeters of aluminum has been found quite sufficient when using 130–140 kv., especially as the dose administered to the skin by this method, owing to the different principle of application, is quite one-sixth less than the full unit skin dose. The use of a light filter also tends to give a more heterogeneous primary beam, a quality that would seem to be desirable in achieving the best results. As soon as the new clinic is complete, a comparison is to be made between the biological or stimulating effect of 130 kv. with a filter of 3 mm. Al and that obtained by 100 kv. using a filter of 1 mm. Al.

(c) *Field—the new wide-angle tube.* The importance of the size of the radiation field has frequently been stressed, how the employment of a large field does not necessarily mean that wide field roentgen therapy is being used. There are many other factors to be taken into consideration.

Owing to the construction of self-protected tube, there has always been the difficulty in obtaining a large enough field at the optimum distance of tube to patient, 17–20 inches. At this distance the limited opening in the shield only allows of a field of approximately 12 inches in diameter. The average length of the trunk that has to be covered is 22 inches. All the more recent investigations, that is during the last six years, have been carried out with the two field method. This means that the dose has been divided fifty-fifty over two overlapping field. Unlike short wave roentgen therapy uniform absorption over the whole area is not necessary. It should be realized that here the object of irradiation is only to produce in the patient a certain "state,"

called saturation, which is indicated by certain post-irradiation phenomena. The wide-angle tube has been so designed that at 17 inches it gives a spread of approximately 22 inches. Time in a busy hospital will thus be saved by the use of this tube, a single field supplanting the double. This method of roentgen application is not unlike that used with ultraviolet rays (Fig. 3).

Optimum Distance of Tube to Patient. From actual experience it has been found that working under the conditions here mentioned the biological or constitutional effect on the patient, on which the results depend, diminishes if the tube is farther than 20 inches from the skin, even though the full number of roentgens are administered. I do not intend to explain this phenomenon.

(d) *Dosage.* The principles of wide field roentgen therapy are so entirely different from those of short wave therapy that there is really nothing in common, except the use of the same agent, so that comparison is made difficult. I have referred to short wave therapy as surgical radiotherapy and wide field radiation as medical radiotherapy. To emphasize further the difference between the rationale of the two methods, and how dosage is dependent on other factors, I am accustomed to compare the pharmacopeial uses of unguentum arseni and liquor arsenicalis. The ointment may contain a sufficiently large amount of arsenic to destroy the tissues. With the liquor, on the other hand, arsenic is given in minute quantities by mouth and yet this may easily produce signs of poisoning. The objects of treatment, the dose and the type of case treated, are so different in these two methods of drug administration that the use of the same therapeutic agent is the only thing in common. Short wave roentgen therapy may be compared with the use of the ointment, and wide field therapy with the use of the liquor.

I have already mentioned that 60–100 r measured in the center of the radiation field represents the average dose required to produce the signs of saturation or of tolerance which are necessary to obtain results. It is wiser to err on the side of under- rather than of over-saturation. In contradistinction to short wave therapy, it is the smaller dose that gives the more satisfactory results. Investigations have so far shown that 100 r per treatment is about the maximum dose necessary although in special cases up to 200 r have been tried. Obviously the roentgens administered by this method are of a different therapeutical or biological value from those registered in short wave roentgen therapy. In the same way as the dose of 600–700 r is with deep roentgen therapy called the unit skin dose, U.S.D., so 100 r might be called with wide field radiation the unit body dose—or preferably, the term total body dose, T.B.D. It is of importance that the hospital roentgenographer be instructed to vary the total body dose according to the reaction noticed by the patient after the previous exposure. It is necessary to keep the patient up to saturation point, neither above nor too far below this level. The radiologist must therefore become more of a physician and less of a technician if he is to obtain the best results. The first dose which should not be more than 60 r is given with the idea of ascertaining the radiosensitivity of the individual. In difficult cases the differential sedimentation test has proved, during

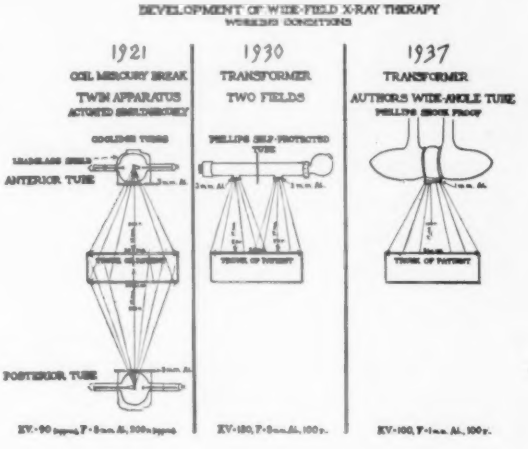

Fig. 3. Development of wide field roentgen therapy, working conditions.

these investigations, to be of considerable value in determining whether saturation or over-saturation has been reached. There is a possibility in some cases of increasing the "negative phase" as it is called, instead of developing the necessary "positive phase." Over-saturation can occur without any uncomfortable phenomena being experienced by the patient.

(e) *Frequency of Irradiation.* The frequency and number of treatments has been found to be dependent on so many factors, such as the type and stage of the disease, age, stamina and debility of the patient, the effect of treatment, etc., that it is not easy to lay down any hard and fast rules.

In one case, for example, the patient is young and there is no time to waste if the condition is to be brought under control, sessions twice weekly for three weeks are then indicated. In another case, we have an elderly woman whose resistance is probably at a low ebb, who will need very careful handling if any benefit is to follow. Here once weekly for six or eight sessions would be advisable. Too frequent irradiation should be avoided.

The object, as far as practicable, is to keep up saturation over a definite period, usually one month. Unless the patient can arrange to attend regularly for a stated period, treatment should be refused or else postponed. Avoid, however, wherever possible the "wait and see" policy, so popular with the patient and his doctor. Procrastination is often disastrous; if it is decided that treatment can be of value, there can be no legitimate reason for delay.

These investigations have clearly shown that once control has been obtained of the pathological condition, this control *should be kept up by carefully planned prophylactic measures.* See that the patient understands the object and importance of these measures. To postpone further treatment until the disease shows clinical evidence of recurrence is not logical or justifiable.

This has been found to be particularly important in blood and glandular conditions like Hodgkin's disease. This work has indicated that carefully planned prophylactic measures and avoidance of overdosage will keep these patients symptom-free and well for many years longer than is possible with other methods of technique.

Unless the patient is prepared to "stay the course" and be under observation for the stipulated period, treatment of the case should not be undertaken.

(f) *Delayed Action.* Patients and the doctors should be warned that the beneficial effect of this method of roentgen application is often delayed for a month or more *after the first course of treatment is completed.* The patient usually expects an immediate and miraculous result. This is unreasonable, considering the disease has probably been progressing for months or even years. This delayed action should be explained, especially as the patient usually feels rather worse at first; there is some stir up of symptoms, and possibly some degree of depression, etc. He is then apt to think the treatment is doing no good. He finds it hard to believe that these signs are favorable. Another point should be made clear to the patient, that relief of symptoms is no criterion as to the effects of treatment. In some cases relief of pain is spectacular and the patient erroneously thinking he is cured, ceases to attend, only to appear in due course with a recurrence.

(g) *Gauging of Results.* It is not easy to determine whether some particular method of treatment is really influencing the disease as a whole—whether it is having just a palliative effect or in fact whether it is doing any good at all. It is obvious, for instance, that in a condition like asthma the fact that the attacks happen to cease with treatment cannot of itself be proof that the disease is being influenced in the slightest degree. The patient has probably had similar intervals of freedom without any treatment. From the commencement of these investigations, special efforts have been made to find some indication of improvement independent of what the patient may say. So that now, in addition to any relief of symptoms or diminution in objective signs, evidence of improvement is looked for in the weight, general appear-

ance, feeling of well-being, alteration in the sedimentation rate—effect on the differential sedimentation test—blood picture, roentgenological changes, etc.

POST-IRRADIATION PHENOMENA AND THE SIGNS OF SATURATION

A number of curious and puzzling phenomena have been noticed during these investigations occurring at different intervals after irradiation. These have been tabulated. Many thousands of cases have now been submitted to this method of roentgen treatment and it is rare for the patient not to mention at least one of these post-irradiation phenomena.

A certain number of these indicate the saturation level. They occur within twelve hours of treatment. Others indicate over-saturation, a condition which is undesirable. The remainder are recorded but their significance is at present unknown. It should be realized that these curious and in many cases bizarre occurrences are quite unexpected by the patient, in fact, it is seldom that they connect them with the treatment. There is no question of suggestion. I am convinced that some day the key to the problem will be found and the explanation of the phenomena will be forthcoming.

The signs of saturation are important to recognize. A curious abdominal sensation, up to slight nausea likened to that of seasickness or pregnancy, is the most common symptom. Then we have giddiness, headache, lassitude and even an uplift as alternatives. An aggravation of symptoms is not uncommon, all usually occurring within twelve hours. The roentgens must be regulated so that none of these signs are excessive—a difference of only 10 r may separate saturation and over-saturation.

To me the most interesting of this list of post-irradiation phenomena is the effect on bowel action. A definite percentage of patients mention a stimulation of bowel action, with others a normal evacuation may become established without aperient. A remark, "I have had a normal action of the bowels, the first for twenty years," is not unusual. Three actions daily may occur but, curiously enough, this increased bowel activity is never accompanied by a griping or abdominal discomfort. In most cases this improvement is permanent, in others it lasts but a few months. Large evacuations and green stools lasting several weeks have also been recorded. Some abnormality in taste is also very frequent, variously described as metallic, oily or just "nasty." A still more interesting observation is the production of a distinctive if unpleasant body odor for some hours after treatment. The patient complains that this is conveyed not only to their clothes but also to their towel and sponge!

As the effect of the irradiation begins to be felt, a definite alteration in mental efficiency is noted, especially in the young. Backward school children become bright; in one instance a girl while undergoing this method of treatment for asthma, passed from the bottom of the class to the top and obtained a scholarship! This interesting effect is to be further investigated. The changes mentally and physically are often very striking.

Increase in weight in the younger patients is found to be an important sign of improvement. This is often remarkable in asthma and spondylitic cases; an increase of two stone in as many months has often been noted. The record increase was in a case of generalized malignant disease, treated by this method for investigation purposes. The weight had been reduced to 6 stone 13 pounds and the patient moribund when first seen; within eight months this had increased to 12 stone and the patient was well.

I consider that each individual has a healthy weight which will not vary as long as he is in health. A loss or an increase of weight may be the only sign of ill health.

EFFECT OF WIDE FIELD ROENTGEN THERAPY IN A VARIETY OF PATHOLOGICAL CONDITIONS

Object. To collect evidence supporting the theory that wide field roentgen therapy creates a constitutional condition, possibly

TABLE I

POST-IRRADIATION PHENOMENA

The following post-irradiation phenomena have frequently been noted while investigating the effects of this method of treatment, in a large number of different types of cases. The significance of these is at present unknown but apparently they are *not* detrimental to the patient.

Gastrointestinal (temporary)

(1) Vague abdominal sensation
(2) Slight nausea
(3) Flatulence and borborygmi
(4) Acute hunger
(5) Thirst
(6) Hiccough
(7) Looseness and regulation of bowel action (frequent and in some cases permanent)
(8) Slight pyrexia
(9) Vomiting
(10) Reduction in abdominal distention
(11) Improvement in digestion (in some cases permanent)

Nervous System (temporary)

(1) Giddiness
(2) Headache
(3) Irritability
(4) Increase of growth of hair on the head
(5) Nervy
(6) Curious tingling of extremities
(7) Flushes
(8) Depression—apprehension
(9) Increase of perspiration
(10) Curious body odor for about twelve hours

Senses (temporary)

Taste	*Smell*
(1) Bad	(1) Distortion and everything smells bad
(2) Metallic	(2) Return after loss in asthma
(3) Coppery	(3) Disappearance of nasal catarrh (asthmatic)
(4) Oily	
(5) Salty	
(6) Acid	

Hearing

(1) May become very acute for one hour or so
(2) Noises in head may disappear for several weeks

Urogenital (temporary)

(1) Frequency of micturition.
(2) Amenorrhea
(3) Painful uterine contractions
(4) Aphrodisiac effect

I have included all those phenomena, however fantastic, that have been noticed by more than three patients. Even so, some are no doubt psychological.

a raising of resistance, that enables the patient to cure himself irrespective of the disease.

The interest in these investigations was greatly increased when it became suspected that this method of roentgen application did not influence the disease directly, but that any beneficial effect depended on the response of the patient.

It was now realized that it might be possible to control disease, not by treating the outward manifestation but simply by stimulating the patient's resistance. New and fascinating possibilities suggested themselves. Table III gives some idea of the amount and type of clinical work covered, and Table IV what remains to be investigated. Owing to the want of facilities, it has only been possible to concentrate on a few pathological conditions, but the results obtained in various diseases mentioned in Table III have been sufficiently interesting and convincing to call for confirmation by those who have the facilities.

TABLE II

POST-IRRADIATION PHENOMENA

(a) *Signs of saturation* or tolerance dose noticed within 12 hours of treatment.

(1) Vague abdominal sensations
(2) Slight nausea
(3) Definite nausea similar to sea-sickness or morning sickness in pregnancy
(4) Giddiness
(5) Headache, frontal
(6) Lassitude
(7) Depression and apprehension
(8) Uplift; feeling of well-being

(b) *Signs of over-saturation* (to be avoided).

(1) Severe nausea
(2) Vomiting
(3) Pyrexia
(4) Loss of weight
(5) Shift to left with differential sedimentation test
(6) A rise in sedimentation rate

(c) *Signs of treatment being ineffective.*

(1) Absence of any signs of saturation irrespective of dose
(2) General deterioration of the patient
(3) Loss of weight
(4) Shift to left with differential sedimentation test
(5) A rise in sedimentation rate

I will briefly give my conclusions on the investigations, extending over some twenty years, into the therapeutic value of the method in a few pathological conditions.

Malignant Disease Group. In cases of cancer mammae, originally devised as a prophylactic measure (1920), wide field roentgen therapy has produced results which, even in the absence of reliable statistics, justify further investigation by some cancer research body.

The few cases of general dissemination such as carcinomatosis, multiple secondary deposits, myelomatosis that have been investigated, have shown remarkable effects, indicating that this method has a very considerable palliative value, provided over-saturation is avoided.

Allergic Group. Asthma, from a chance observation in 1922, was the first benign condition found to respond to this method. Considerable research work in this condition has been possible during the last few years. I have come to the conclusion, after treating a large number of these cases, that there can be no question that in the uncomplicated allergic type the results are so satisfactory and certain that the method must eventually come to be established as a routine treatment measure. It has already been introduced with success in several hospitals. On the technical side these investigations have shown that the results are more satisfactory if the thorax is *entirely eliminated* from the radiation field. Over-saturation must also be carefully avoided.

Rheumatism Group. Investigations into the effect of wide field roentgen therapy on this group have extended over a period of six years. I am convinced it must prove of definite value in certain varieties of chronic generalized rheumatism. However, for various reasons, it was decided to limit the investigation to one type, namely the ankylosing spondylitis or spondylitis adolescens, the spinal arthritis that attacks young adults, usually an athlete in his prime. Four hundred patients have been investigated clinically and roentgengraphically. It is necessary to mention the final conclusions as being of some importance. The onset of this disease can now be detected clinically and roentgenographically five to seven years *before* the onset of spinal pain and stiffness: (*a*) *clinically*, by *recurrent* attacks in early life of rheumatic pain in the limbs, joints, thorax and abdomen, but not in the back or sacroiliac joints; (*b*) *roentgenographically*, by progressive pathological changes in the sacroiliac joints (sacroilioitis) during this period.

It has been shown that if wide field roentgen therapy is used during the prespondylitic period, that is *before* the spine is involved, there is no reason why this tragic disease should not be wiped out. This conclusion is based on results, many of which have been remarkable, noted while investigating the effects of the method in about 200 cases. This is by far the most important practical result that has yet emanated from these investigations; they are being continued.

This disease is not rare but it is not being recognized or treated in its early stages. Whenever a healthy youngster complains that he is "rheumatic," always suspect changes in the sacroiliac joints, now known to be associated with an early spondylitis.

Rheumatoid Arthritis. A few cases have been investigated of this type of arthritis which should theoretically respond to this method of roentgen application. The results certainly tend to confirm this. Given facilities, this is the next piece of work to be carried out.

Diseases of the Blood and Lymphatic Glands. Investigation in this group has shown that life can be prolonged and the patient will remain symptom-free nearly four times as long when wide field therapy is used as with any *local* method of roentgen-ray application. Over-saturation should be avoided as well as too frequent irradiation. An occasional dose as a prophylactic measure is essential even in the absence of symptoms.

The majority of diseases mentioned in

TABLE III

DISEASE GROUPS SO FAR INVESTIGATED BY WIDE FIELD ROENTGEN THERAPY, 1920–1938

xxx Over 100 cases treated.
xx Under 100 cases treated.
x Under 12 cases treated.

Allergic Group

xxx Asthma
x Urticaria
x Migraine

Endocrine or Metabolic Group

x Backward children

Lymphatic Gland Group

xx Hodgkin's disease, lymphadenoma and allied conditions
x Lymphosarcoma

Blood Group

xx Leukemia (typical and atypical)
x Polycythemia

Neuroses Group
(? Endocrine Imbalance)

x Functional or the neurotic
x Phobias
x Menopausal
x Functional backache
x General debility

Rheumatic Group

x Spondylitis osteo-arthritica
xxx Spondylitis adolescens or ankylosing spondylitis
x Rheumatoid arthritis
xx Fibrositis
xx Rheumatic backache—lumbago
x Polyarthritis and periarticular rheumatism

Chronic Infective Group

x Osteomyelitis
x Chronic septic conditions

Skin Group

x Psoriasis
x Multiple warts
x Fibromata
x Generalized eczema and furunculosis
x Alopecia

Malignant Disease Group

xxx Prophylactic
x Carcinomatosis
x Myelomatosis

Tables III and IV are definitely outside the scope of deep roentgen therapy. This fact alone must make it clear that an entirely new field in radiotherapeutics is opened up. Needless to say, much of this work needs confirmation by others. However, these investigations have produced sufficient evidence to support our original contention and at least indicate the lines along which work should continue.

So few cases have been investigated in the other groups mentioned in Table III that no conclusions are possible. These tables should be studied by those anxious to prove that it is possible to influence disease through altering the patient's makeup.

TABLE IV

CASES NOT YET INVESTIGATED, BUT THEORETICALLY SHOULD RESPOND

Endocrine or Metabolic Group

Abnormal loss or increase of weight without cause especially in children
Abnormal growth or defective development of children (not congenital)

Blood Group

Hemophilia
Leukopenia
Certain anemias

Neurosis Group

Mental defectives
Enuresis

Acute Infective Group (Generalized)

Pyemia
Septicemia

Ductless Gland Group

Diabetes
Hyperthyroidism
Hypothyroidism

Deficiency Diseases

Rickets
Osteomalacia

SUMMARY

(1) A description is given of the development of a method of roentgen-ray application called wide field roentgen therapy.

(2) Investigations extending over a period of some twenty years into the value of this method in a variety of pathological conditions are outlined.

(3) It is pointed out how the principle of the method is entirely different from

that of short wave or deep roentgen therapy.

(4) It is shown how irradiation of the whole trunk by roentgen rays of low intensity in small doses produces constitutional rather than local effects.

(5) The result would appear to be a raising of the general resistance to disease, comparable to the effects of ultraviolet, or sunlight, only a hundredfold more effective.

(6) A theory as to how this effect is being obtained is put forward.

(7) In order to appreciate the gap that exists between the two methods, deep therapy is denoted as *surgical* radiotherapy; wide field radiation as *medical* radiotherapy.

(8) The method was originally designed as a prophylactic measure in malignant diseases.

(9) Results obtained in large numbers of cases clearly indicate that work in this direction should be continued by some cancer research body.

(10) Certain blood tests—the sedimentation rate and the newer differential sedimentation test—have enabled the constitutional effect of irradiation on the patient to be recorded. This has led to a rapid development during the last six years in the treatment of pathological conditions other than cancer.

(11) This method of roentgen-ray application has been tried out, on a limited scale, in many diseases with very interesting results.

(12) These results indicated that they were being obtained through some general influence on the patient rather than through any direct effect on the objective signs of the disease.

(13) Investigations now show that it is possible to influence pathological conditions hitherto quite outside the scope of short wave roentgen therapy or in fact any form of local applications of roentgen rays.

(14) Owing to the want of facilities and funds, investigation into the value of this method has had to be limited. The material being available, chronic rheumatic conditions, ankylosing spondylitis and asthma have been mainly dealt with. The first practical result of this investigation is that a serious rheumatic condition, known as ankylosing spondylitis or spondylitis adolescens, will eventually be eradicated.

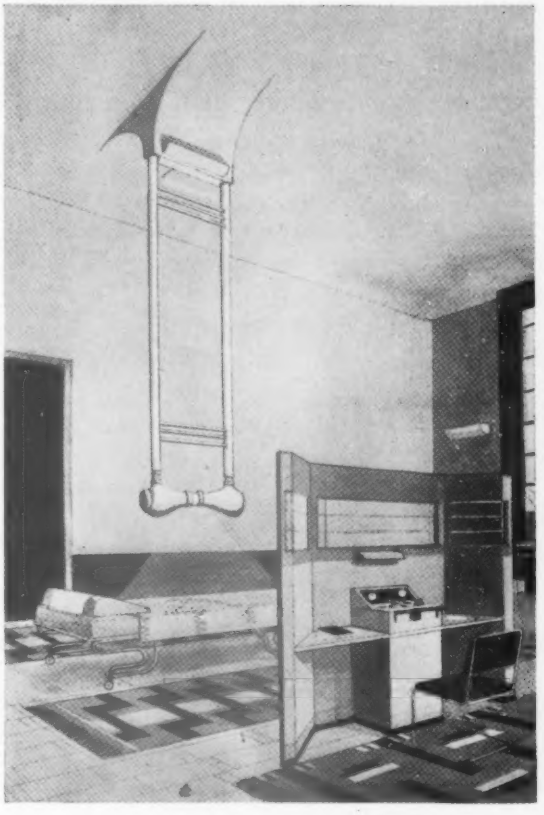

Fig. 4. Drawing of wide field roentgen therapy department at the Charterhouse Clinic, showing the wide-angle roentgen tube.

(15) The center for this research work has of late years been at the Charterhouse Rheumatism Clinic, London.

(16) For technical reasons, a new wide-angle roentgen tube has been designed by Philips, for this method of roentgen-ray application.

(17) It enables the whole trunk to be irradiated at the optimum distance of tube to patient of 20 inches. This tube, is to be installed at the new Charterhouse Rheumatism Clinic where this work is to be continued (Fig. 4).

(18) The technique is described and how the signs of saturation or tolerance can be

recognized by certain post-irradiation phenomena.

(19) A list of remarkable as yet unexplained post-irradiation phenomena is given.

(20) The beneficial effects on the patient with wide field roentgen therapy as registered by the blood, weight, general health and the improvement mentally and physically are discussed.

(21) Owing to the smallness of the dose administered, 60–100 r, there are no dangers or possibilities of damage to the patient as long as the rules of technique are adhered to.

(22) A report is given with conclusions on the various investigations that have been carried out in the last twenty years into the influence of wide field roentgen therapy on disease generally. Tables of diseases are given.

(23) It is stressed that this work is far from complete, but it is felt that a report should now be published so that other workers may be stimulated to give the method a trial.

(24) The place that this therapeutic method takes in medicine must in the future be entirely dependent on the clinical results obtained.

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THE COMBINED ROENTGEN AND RADIUM TREATMENT OF CARCINOMA OF THE CERVIX*

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IN 1937, we reported the results of combined roentgen-ray and radium treatment in 70 cases of carcinoma of the cervix.[5] These cases were irradiated at the Pondville Hospital at Norfolk (Massachusetts Department of Public Health) and were followed for three and a half years after treatment. All patients showing evidence of disease at the end of this period were classified as dead. The cases were chosen without selection, the only prerequisites being that there should have been no previous irradiation and no operative procedure.

The method of irradiation employed was as follows: Roentgen rays generated at 200 kv. with a filtration of 0.5 mm. of copper were applied at a distance of 50 cm. to each of four pelvic portals, two anterior oblique and two posterior oblique. The size of these portals was either 8 by 10 cm. or 10 by 10 cm. Distances greater than 50 cm. were employed in a few cases, but it was felt that the depth dose was not sufficiently increased to warrant the extra expenditure of energy. Furthermore, experiments with filters heavier than 0.5 mm. of copper showed no clinical increase in skin tolerance, and there was only a 2 per cent increase in the 10 cm. depth dose. The results of these experiments with filtration are now in press.[1]

Daily treatments of from 300 to 600 r (air measurement) were employed, alternating the fields so that a given area was exposed every fourth day. Each field received a maximum of 1,500 to 2,000 r, the total dosage depending upon the rapidity with which the treatment was given and the general reaction of the patient. In most instances daily exposures of 400 r were administered, the series being completed within three weeks. A few days following the roentgen therapy, heavily filtered radium was applied within the uterine canal, two doses of 1,500 millicurie- (milligram) hours being given four days apart. In all instances, a biopsy was taken before the roentgen therapy, after completion of the roentgen series, and after the first radium application. There was no consistency in the grading of the tumors, and frequently all three grades of carcinoma were found in the same tumor at different stages of treatment. Those tumors which after the roentgen treatment showed microscopically "radium reaction only" gave the best results. It is believed that the biopsy following the completion of the roentgen series may prove of considerable prognostic value.

TABLE I

	Total Cases	3½ Year Survival	Percentage
Roentgen rays and radium	70	25	35.7
Radium alone	150	38	25.4
Surgery alone	60	23	38.3

For comparison with this series of 70 cases treated by the method of combined roentgen and radium irradiation, a series of 150 cases treated by radium alone, and also 60 cases operated on without irradiation were reviewed. The three and a half year results are shown in Table 1. It will be noted that the 35 per cent salvage by combined roentgen and radium treatment is 10 per cent better than that obtained by radium alone, and nearly equals the results in the small selected group subjected to hysterectomy.

* Read at the Thirty-Ninth Annual Meeting, American Roentgen Ray Society, Atlantic City, N.J., Sept. 20–23, 1938.

A classification according to the stage of the disease is shown in Table II. Although the radium dose was smaller when combined with roentgen irradiation than that employed when radium alone was used, the figures show a 100 per cent survival of the A and B cases. This indicates that sufficient radiation was delivered by the combined method to satisfactorily control disease limited to the cervix or in close proximity to the cervix.

Because of the rapid falling off of intensity by the inverse square law, the amount of radiation delivered at a distance of 1.5 to 2 cm. by 3,000 mc-hr. of radium is hardly sufficient to control epidermoid carcinoma. Therefore, we cannot expect to be successful in combating disease which has extended beyond the cervix by the use of an intrauterine applicator alone. The intravaginal application of radium may be helpful in these cases, but is often technically difficult. The use of roentgen rays externally will augment the radium dose in the peripheral portions of the pelvis, and theoretically should result in a cure of a greater percentage of the more advanced cases. The improved results in the B and C groups obtained by the combined method as compared with radium treatment alone substantiate this theory. The D cases thus far have proved hopeless from every therapeutic standpoint.

The three and a half year results reported in the original communication have recently been brought to five years with only a 2 per cent difference in the total salvage. This would indicate that most of the patients who die after irradiation of cancer of the cervix do so within the first three and a half years, and that for statistical purposes it is not essential to wait for five year results.

During the winter of 1936, a machine became available at the Collis P. Huntington Memorial Hospital for supervoltage roentgen therapy. This apparatus was designed and built by the High Voltage Research Group at the Massachusetts Institute of Technology, and has been fully described in previous communications.[3 4 6]

Fifty-nine cases of carcinoma of the cervix have thus far recevied supervoltage treatment. Approximately half of this number (28) had been treated previously with lower voltage roentgen rays or radium, and were given supervoltage radiation as a palliative measure without hope of cure.

TABLE II

	A	B	C	D
Roentgen rays and radium	5	3	45	17
Radium alone	15	13	100	22
Surgery alone	28	11	20	1
	$3\frac{1}{2}$ Year Survival			
Roentgen rays and radium	5—100%	3—100%	16—35.5%	1—5.8%
Radium alone	12— 80%	7— 53.8%	18—18%	—
Surgery alone	13— 46.4%	5— 45.5%	5—25%	—

In 31 cases without previous irradiation, a plan of therapy analogous to that used in the Pondville group was carried out. Although the supervoltage dosage was kept reasonably uniform in this group, the radium dosage was varied from 3,000 to 4,000 mc-hr. In many instances, an intravaginal application of radium was made in addition to the intrauterine treatment. The roentgen apparatus was operated at 1,000,000 volts constant potential, with a focal skin distance of 70 cm., and filtration equivalent to 4 to 6 mm. of lead; half-value layer of copper 10 to 11 mm. In a few instances the radium treatment was given before the roentgen treatment, but in the majority of cases the roentgen therapy preceded the radium.

The combined supervoltage and radium

treatment of carcinoma of the cervix has been in use for only eighteen months, and sufficient time has not elapsed for the accumulation of statistical data. However, certain differences between this type of therapy and that employing 200 kv. rays have become apparent. These differences may be classified under skin reaction, effect on the general condition of the patient, reaction of the deep-lying normal structures, and effect on the tumor.

The practice of expressing roentgen dosage in terms of roentgens measured in air has given rise to some confusion. It should be kept in mind that the amount of radiation which the skin receives consists not only of the primary beam, but is augmented by rays which reach the surface through back-scattering. There is a marked difference in the back-scattering from rays produced at 200 kv. as compared with those generated at 1,000 kv. If 10 by 10 cm. fields are employed, about 30 per cent of the skin dosage is derived from back-scatter with 200 kv. rays, and only 10 per cent of the skin dose is due to back-scatter with 1,000 kv. rays. It has been stated that the majority of patients treated at 200 kv. received 400 r per day, air measurement, through 10 by 10 cm. portals. Each of four fields, two anterior oblique and two posterior oblique, was treated with this dosage on consecutive days until each field had received a total of 2,000 r; that is, the entire skin dosage administered on completion of the series was 8,000 r, air measurement. However, if the amount of radiation due to back-scatter is added, disregarding the exit dose which is small at 200 kv., the daily dose per portal becomes approximately 570 r, and the total dose per portal is approximately 2,850 r. The aggregate skin dose, measured with back-scatter and including all four portals, amounts to about 11,400 r.

Most of the patients thus irradiated developed severe erythemas, and a larger dosage was not considered safe because of the skin reaction. At one time discrepancies were noted in the severity of the skin reactions, which were attributed to variations in the output of the roentgen apparatus due to fluctuations in the line voltage. When this condition was remedied, the skin reactions became more uniform.

Those patients irradiated on the 1,000,000 volt unit were treated through three portals, measuring either 10 by 10 cm. or 12 by 12 cm., one directly anterior above the symphysis and two posterior oblique. The daily dose per portal, measured in air, was 400 r, and a total of 2,000 r was given to each portal. The total dose administered to the skin, including the three portals, was 6,000 r. If one includes the back-scatter, the daily dose per portal is approximately 440 r at 1,000,000 volts, as compared with 570 r at 200 kv. This makes the total skin dose with back-scatter 2,240 r per portal on the supervoltage unit, as compared with about 2,850 r per portal on the 200 kv. unit. At the conclusion of the series, the patients irradiated on the supervoltage unit received a superficial dose of approximately 6,700 r to the skin, as compared with 11,400 r on the 200 kv. unit.

The tolerance of the skin to 1,000,000 volt roentgen rays as compared with 200 kv. rays is approximately double when comparative ionization measurements are made in air. This discrepancy becomes less when measurements are made on the patients' skin or on the surface of a phantom, but there is still a pronounced difference in favor of the shorter wave lengths. A few of the patients irradiated on the supervoltage unit, using the technique which has been outlined, have shown faint reactions over the posterior oblique areas, but most of them have shown no reaction at all. Over the anterior area, however, a moderately severe erythema almost always develops, which may be attributed chiefly to the exit dose. This dose has been measured on a large group of patients and has been found to average 25 per cent of the intensity delivered initially to each portal on the opposite side of the pelvis. In other words, the anterior area receives 50 per

cent more radiation than either of the posterior oblique areas. In no case has this reaction caused the patient any great discomfort, and the erythemas have all disappeared with the usual subsequent tanning and epilation. The portals of entry have been so planned that the erythema develops anteriorly rather than posteriorly where a reaction, particularly between the gluteal folds, may occasion severe discomfort.

Supervoltage radiation has been tolerated rather better than that administered at lower potentials. Many patients in the 200 kv. group suffered from roentgen sickness. Although roentgen sickness has by no means been absent in those patients treated at the higher voltage, it has been definitely less frequent and less severe. There is a logical explanation for this. There seems to be a relationship between roentgen sickness and the volume of tissue irradiated. We are less likely to have generalized reactions when small portals of entry are used than when large fields are treated. It has already been pointed out that the scattering from the shorter wave length beam is much less than from the longer wave lengths. Because of the diminished scattering, the amount of tissue irradiated on the supervoltage unit is limited more closely by the size of the portal of entry than is the case at lower voltage.

The inhalation of ozone also plays a rôle in the production of generalized roentgen reaction. The supervoltage treatment room is completely separated from the compartment in which the voltage is generated. Moreover, ventilation is obtained by drawing fresh air from outside the building. The presence of ozone is in this manner completely eliminated.

Because of the lessening of roentgen sickness, it is possible to treat many cases on the million volt unit as out-patients, who otherwise would have to be hospitalized.

Routine blood counts have been carried out at the beginning and end of the radiation series. Those patients who are anemic at the outset are likely to do badly no matter what type of radiation is given. However, when small portals are used, we have noticed no greater untoward effect on the blood from the supervoltage rays than we have from the lower voltage rays. It has rarely been necessary to discontinue treatment because of a fall in the white blood count.

It is perhaps unnecessary to mention that in expressing depth dose in roentgens we deal in percentages of the dose measured at the surface with back-scattering and not with measurements made free in air. We have carried out comparative studies between 200 kv. depth doses and 1,000 kv. depth doses, measurements being made not only in the phantom, but also on cases under routine treatment for carcinoma of the cervix with the ionization chamber in the vagina. In the average female pelvis approximately one-third of the surface dose reaches the region of the cervix with 200 kv. radiation, and about 50 per cent of the surface dose is delivered at 1,000,000 volts. With the method of radiation which we have described, the cervix receives an average dose of 190 r per day when irradiated at 200 kv., and approximately 220 r per day at 1,000,000 volts. The total tumor dose delivered in the lower voltage series was about 3,800 r. As already stated, treatments were given to each of four portals on consecutive days, usually including Sunday, so that the entire series was completed in twenty days. In the higher voltage group, daily doses were given to each of three portals, instead of four portals, and the total tumor dose averaged about 3,300 r. Treatments were not given on Sunday in the latter group and it therefore took seventeen days to complete the series. Thus, at 1,000,000 volts we have delivered a tumor dose some 400 to 500 r less than the dose administered at 200 kv., and in a slightly shorter period.

In the lower voltage group, no deep-seated reactions such as diarrhea and vesical irritation developed as a result of the

roentgen treatment. The total amount of roentgen radiation delivered was limited only by the skin reaction. On the other hand, the supervoltage group has shown a different response. Most of the patients have developed diarrhea toward the end of the series, and many have had tenesmus with frequency and urgency of urination. A few have passed small amounts of blood in the stool. These sequelae are not always present, for in a number of instances the patients have had no complaint whatsoever, and in an occasional case constipation rather than diarrhea has been noted. In supervoltage treatment such as we have employed, it is apparent that we can no longer be guided by the tolerance of the superficial tissues, but must determine the amount of radiation which can safely be given by the reaction in the deeper structures of the pelvis. This is particularly true when small multiple portals of entry are employed. It is well established that increasing the size of the portal of entry increases the depth dose of 200 kv. radiation, but the depth dose at the higher voltage is much less affected by the size of the field. It is important that the fields irradiated be large enough to include all of the disease-bearing area, but we believe it is bad technique to use excessively large portals merely to increase the depth dose.

It is difficult to explain the appearance of deep-seated reactions in the pelvic cases treated by supervoltage radiation. To be sure, the daily tumor dose has been slightly greater than that administered at 200 kv., but the total dose has been somewhat smaller. The slight difference in time element does not offer a satisfactory solution. It is possible that the thimble chamber does not give us an accurate intensity measurement of the shorter wave lengths, and that we are in fact administering larger doses than our ionization measurements indicate.

A difference in biological reaction may be advanced as another hypothesis. In support of this, we have some experimental data. Work done in collaboration with Dr. John C. Larkin, Resident in Radiology at the Peter Bent Brigham Hospital, Boston, has shown that *Drosophila* eggs placed at various depths in a phantom are more readily killed by 1,000,000 volt rays than by 200 kv. rays.

The 31 cases which received supervoltage radiation are classed in Table III according to the stage of the disease. The follow-up period is too short to afford any statistical value. There have been more favorable cases in the later series than in the group irradiated at the Pondville Hospital.

Table III

	No. of Cases	Immediate Regression
A	11	10—90%
B	5	4—80%
C	12	9—75%
D	3	1—33%

Satisfactory regression of the disease has been observed in all but one of the Group A cases. This patient, aged sixty-four, was first seen in September, 1937, at which time the cervix was enlarged and involved in a fibrous type of new growth. There was no extension to the vaginal walls, and the body of the uterus was freely movable. No masses could be felt by rectum. The uterocervical segment was broad and edematous. The first biopsy was reported as adenocarcinoma. The patient was given supervoltage radiation during October, and received additional moderate roentgen treatment during November. The second biopsy at the time of radium treatment in December was reported as epidermoid carcinoma, Grade 3. Clinically, the growth had shown considerable though not complete regression from roentgen treatment alone. The patient died outside the hospital about six weeks after the application of radium. Death, as reported by the city clerk, was due to carcinomatosis. Further details are not known. This patient received rather more than the usual amount of roentgen therapy, and the radium dose

was somewhat in excess of 3,000 mc-hr. It seems unlikely that a patient whose local condition was so satisfactory at the time of radium application should have a sufficiently rapid extension of malignant disease to cause death within six weeks. A complicating factor in this case was the presence of diabetes. It is not improbable that this patient's death was not the result of malignancy, but due to the advent of infection, to excessive irradiation, or to a combination of both.

Another patient in the A group received supervoltage therapy without radium. All clinical evidence of disease had disappeared six weeks after completion of the irradiation series, and a month later a complete hysterectomy was performed. Microscopic examination of the cervix after removal showed persistent Grade 2 epidermoid carcinoma. This substantiates our belief that the dosage thus far administered by supervoltage roentgen rays alone is not sufficient to permanently control deep-seated carcinoma.[2]

Of the Group B cases, 4 have done well. The fifth was reported on August 6, 1938, as dying. This patient was thirty-seven years of age, and in October, 1937, showed an enlarged cervix involved throughout with an irregular new growth. There was extension to the vaginal wall on the left side. The uterocervical segment was large and edematous, but quite movable. The patient's general condition was not good. The biopsy report was epidermoid carcinoma, Grade 2. The growth showed little, if any, regression following the supervoltage series given in November, and through some misunderstanding the patient did not receive radium treatment until the latter part of January, at which time it was felt that the case was beyond salvage.

In the C group, 9 cases have shown satisfactory immediate regression. One is dead, another is doing badly and will probably die, and the third patient, irradiated in June, has not returned for follow-up examination.

One of the 3 Group D cases is dead. A second case, recently treated, showed complete softening of both broad ligaments and disappearance of the vaginal wall extensions following supervoltage radiation. A month after radium treatment there was no palpable evidence of active disease. The third Group D case was considered too far advanced for irradiation of any kind, and it was only on the insistence of the patient's husband that supervoltage therapy was instituted. The response to roentgen treatment was so satisfactory that radium was subsequently given. The pelvic symptoms returned about seven months after irradiation, and the disease again became active. This patient is receiving further roentgen therapy.

DISCUSSION

The combined roentgen and radium treatment of carcinoma of the cervix is not presented as a new method. This regimen has been used by other workers in the field of cancer therapy to good advantage. The results observed at the end of three and a half years are encouraging, and these have remained practically unchanged at the end of a five year follow-up period.

Whether or not supervoltage radiation will improve our end-results, we are not at present in a position to say. There are, however, several immediate advantages to be ascribed to the higher voltage therapy. When multiple small portals are employed, the total depth dose which can be delivered at 200 kv. is limited by the reaction of the skin rather than by any untoward effect on the deeper structures. The reverse is true with 1,000,000 volt therapy. The physiological depth dose obtained from the shorter wave lengths is greater than that measured by the thimble ionization chamber, and symptoms of rectal and bladder irritation, which were lacking in the 200 kv. group, have developed in the 1,000 kv. group. The patients have tolerated the supervoltage treatment rather better than the 200 kv. radiation as far as roentgen sickness is concerned.

It is our belief that the dosage thus far administered to the center of the pelvis by

external roentgen irradiation alone is not sufficiently large to permanently control epidermoid carcinoma. With one possible exception, we are not aware of having produced any serious radiation damage with the supervoltage unit. The possibility, however, of late untoward radiation changes looms ever before us, and we therefore feel that great caution must be observed in increasing the dosage. We think that larger amounts of supervoltage radiation than we have thus far administered will eventually be given with safety.

Radium is most likely to fail when parametrial extension of carcinoma of the cervix has occurred. In such cases, it might be well to place our chief reliance on heavy external irradiation, augmented by a small radium dose. On the other hand, in those cases where the disease is limited to the cervix, or has extended slightly beyond the cervix, a modification of technique consisting of a relatively large dose of radium and less roentgen therapy seems logical. Radium has proved so efficacious in the treatment of carcinoma of the cervix that in the present stage of development of our technique of external irradiation we do not feel justified in discarding it entirely.

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DISCUSSION

Dr. William P. Healy, New York City. I would like to commend the reader of the paper and his associates upon their conservative attitude. This is just a report of progress on their part, and in a general way it verifies what has been done for a great many years throughout the country and elsewhere in the use of combined radiation methods of therapy for cancer of the cervix.

For about eighteen years, I have been carrying out combined methods of radiation therapy for cancer of the cervix at the Memorial Hospital through the cooperation of the roentgen-ray department. At first low voltage roentgen therapy, always preceding the radium, was used, but since 1926, we have used high voltage, the 200 kv. During most of that time until about four years ago, we used only four portals, two anterior and two posterior, as has been done by these authors. But for the past four years, we have increased the number of portals to six.

Another point which might be discussed is that with the supervoltage, as utilized by Dr. Dresser and his associates, they have employed one anterior field, the suprapubic field, and two oblique posterior fields, with the anterior field perpendicular. That was done undoubtedly so as to concentrate the rays, the central beam, upon the cervical field, but nevertheless it does concentrate it also upon the rectum and the bladder, and this must result in vesical and rectal irritation, both primary and secondary. The primary symptoms clear up rather quickly but the secondary symptoms may be very unfortunate. These patients may a year or longer after this supervoltage therapy, with the fields set up so that they cross-fire on the rectum and the bladder, have very serious bladder or rectal radiation lesions.

I believe that the plan which we are following at the Memorial Hospital is superior, in which we set up the four to six fields so they are perpendicular to the surface of the body; the beam is perpendicular and goes directly to the parametrium. We want the parametrial field and not the cervix irradiated by the roentgen rays. We plan to take care of the cervical field, the primary lesion, with radium. By setting up the fields perpendicularly, you avoid damaging the bladder and the rectum to the same degree that will occur when you set them up obliquely. We formerly did set up ours obliquely but because

of the sharp proctitis and cystitis which resulted in so many cases, we have omitted doing that.

Dr. Dresser stated that in their cases they apply the radium one week after the termination of the roentgen therapy. We believe that is too soon. Actually, they have not yet obtained in the irradiated fields the full radiation reaction that they are going to get in the tumor-bearing area from the roentgen therapy that has been delivered. When they then apply radium on top of it, their patients are much more apt to have severe rectal reactions, rectal ulcers or bladder reactions, than they will have if the application of radium is delayed until approximately three or four weeks after the termination of the roentgen therapy.

Those are very important points for the patient's protection and they do not interfere with the salvage in taking care of the disease. We also believe that roentgen therapy should always be given first. I cannot agree with Dr. Dresser that three and a half years is enough time to depend on and that thereafter the cases that are well at three and a half will remain well for five. His series, as he says, was quite small in number; five and three in one group and only one or two out would ruin it. He must wait at least five years and then he will find, even after five years, they will keep falling off from disease, from cancer.

The plan we follow is roentgen irradiation first and then two to four weeks later, radium. Our present method of roentgen irradiation is the pyramidal dose method. We begin with 100 r to each of two opposite fields daily, using six fields. It take three days to go around the pelvis. Then the next cycle is at 150 r and the third cycle is at 200 r to each of two opposite fields; the fourth at 250 r; the fifth at 300 r; the sixth at 350 r, to each of two opposite fields; and the seventh at 350 r. It takes about twenty-one days and at the end of that time the patient has received 1,700 r to each of the six fields with a 200 kv. machine, 70 cm. target-skin distance, and we believe the 70 cm. is better than the 50 cm. They stand it remarkably well. During that time, all these treatments are given with the beam perpendicular, not oblique. Nevertheless, since the cervical field and the tumor field in the cervix is taken in tangentially with the anteroposterior and the posteroanterior treatments, and directly with the lateral treatments, you can see the cervical lesion disappear so that at the end of three weeks, you will have comparatively little primary lesion still evident in the cervix. Then you must wait, as I said, two to four weeks before applying radium.

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THE ROENTGEN DIAGNOSIS AND THERAPY OF RETROPHARYNGEAL ADENITIS*

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RETROPHARYNGEAL adenitis and abscess are fairly common conditions, occurring most often during the first year of life and rarely after the age of three. The roentgen diagnosis of an abscess is easy in most instances, as pointed out by Pancoast and Pendergrass,[4] but adenitis or early abscess is often difficult to diagnose because of the normal variations in the size of the retropharyngeal space caused by respiration. Hay[1] studied lateral roentgenograms of the pharynx *at rest* in 25 normal children varying in ages from three weeks to fourteen years. Because of the difficulty in obtaining roentgenograms of the pharynx *at rest* in the uncooperative child, we have adopted a simple procedure for examining and differentiating between the normal and the widened retropharyngeal space. We have reviewed a series of lateral roentgenograms of the nasopharynx in 80 infants from birth to three years of age and our purpose is to present both the normal and the pathological findings.

ANATOMY

The retropharyngeal space lies anterior to the vertebral column and extends upward to the base of the skull. Its downward extension, the retro-esophageal space, communicates with the postpericardial mediastinum. This space contains a network of loose areolar tissue so that in the cadaver the pharynx and esophagus may be easily separated from the prevertebral fascia. It is enclosed anteriorly and posteriorly by two layers of fascia which blend laterally with the sheaths of the great vessels. There is a chain of medial and lateral lymph nodes in the retropharyngeal space. In early life the number of nodes may vary from three to ten but in adult life there are rarely more than one or two as the medial nodes undergo atrophy. The retropharyngeal nodes are the lymphatic drainage areas for the nasal accessory sinuses, the nasal fossae, the pharynx, the larynx and the middle ear. An initial infection arising in any of these regions may be transmitted through the lymphatics to the retropharyngeal space and extend on downward to the peribronchial nodes or posterior mediastinum. The faucial tonsils have no direct connection with the retropharynx, but drain directly into the deep cervical glands.[3] The efferent lymphatics from the retropharyngeal lymph nodes may also drain into the deep cervical glands adjacent to the internal jugular vein, so that glands palpable along the border of the sternomastoid muscle may receive their infection from either the tonsils or the nasal accessory sinuses and nasopharynx.

CLINICAL CONSIDERATIONS

A retropharyngeal abscess usually develops from suppuration and breaking down of the retropharyngeal lymph nodes which have become involved due to an infection in the upper respiratory system. The occasional exceptions to this mode of origin are those cases wherein a foreign body has punctured the retropharyngeal or retro-esophageal space. If an infant or child has difficulty in breathing or nursing following an upper respiratory infection, a retropharyngeal swelling with its primary focus in the sinuses, ears or adenoids, as well as an enlarged thymus or pulmonary pathology, must be considered.

ROENTGEN DIAGNOSIS

Since the observations on enlarged thymus by Pancoast and Pendergrass,[4] we have included a lateral view of the nasopharynx and chest as a part of the thymus examination in infants. Our routine examination of the sinuses includes a lateral view of the nasopharynx to exclude a retro-

* From the Radiological Clinic of Drs. Groover, Christie and Merritt.

TABLE I

THE NORMAL RETROPHARYNGEAL AND RETROTRACHEAL SPACE

Exposure during Inspiration	28–48 inch Target-Film Distance					
Age	Under 1 year		1 to 2 years		2 to 3 years	
No. of cases	40		19		21	
	Retro-pharyngeal	Retro-tracheal	Retro-pharyngeal	Retro-tracheal	Retro-pharyngeal	Retro-tracheal
Extremes	11–3 mm.	18–8 mm.	11–4 mm.	16–8 mm.	11–3 mm.	14–8 mm.
Average	7 mm.	10 mm.	8 mm.	11 mm.	8 mm.	10 mm.

pharyngeal swelling. Because the normal retropharyngeal space varies greatly with the phase of respiration, we exclude this variable factor by making all lateral examinations of the pharynx, neck and chest during inspiration, and to stop motion the time factor is never more than 1/20 and often 1/40 of a second. We have reviewed a series of lateral roentgenograms of 80 apparently healthy children *during inspiration* to determine the width of the retropharyngeal and retrotracheal spaces. The film target distance has varied from 28 to 48 inches. Measurements were made from the body of the second cervical vertebra to the adjacent posterior pharyngeal wall for the retropharynx. The retrotracheal measurements were made from the posterior tracheal wall just below the larynx to the nearest adjacent vertebral body. The results of these measurements are shown in Table 1.

The normal retropharyngeal space in infants and young children never measures over 11 mm. during inspiration using ordinary roentgenographic distances. The retrotracheal space varies somewhat with age, measuring not over 18 mm. up to one year, not over 16 mm. from one to two years and not over 14 mm. after the age of two. If the pharyngeal air space measures less than 15 mm. it should be suspected that the roentgenograms have not been taken during inspiration and the patient should be re-examined. With very large retropharyngeal swellings the pharyngeal air space may be partially obliterated even during inspiration, but this is usually easily recognized, as the tongue is pushed forward.

In the past two years we have diagnosed retropharyngeal adenitis in 20 children. It was impossible in a few cases to differentiate between a cellulitis and an adenitis. There have also been 3 cases of retropharyngeal abscess with definite fluctuation on digital examination. These 3 cases offered no difficulty in diagnosis and are not considered in this report, as once suppuration begins the problem is entirely surgical. Table II shows the clinical diagnosis and age in these 20 cases.

As shown in Table II the clinical diagnosis in 6 cases was a nasopharyngitis or sinus disease. Not only did these 6 cases

TABLE II

CLINICAL DIAGNOSIS IN 20 CASES OF RETROPHARYNGEAL WIDENING

Diagnosis	No. of cases	Age
Nasopharyngitis or sinus disease	6	8 mo. 16 mo. 18 mo. 18 mo. 19 mo. 24 mo.
Enlarged thymus	5	4 wk. 5 wk. 6 wk. 3 mo. 12 mo.
Otitis media	4	7 mo. 9 mo. 10 mo. 20 mo.
Foreign body	2	14 mo. 19 mo.
Unexplained fever	1	19 mo.
Cervical adenitis	2	2½ yr. 3 yr.

have roentgen evidence of sinus disease but all 20 cases showed the antra or ethmoid sinuses to be entirely opaque or have a marked thickening of the lining mucosa. We are impressed with the frequency with which a nasopharyngitis in infants and children is followed by a sinus infection, and occasionally a retropharyngeal adenitis or cellulitis.

In 5 cases the clinical impression was enlarged thymus, because of the age of the patients, the difficulty in breathing and the attacks of cyanosis. The roentgen examination showed the thymus to be normal in size, both in the anteroposterior and lateral views, and the symptoms were due entirely to a retropharyngeal or retrotracheal swelling. On digital examination there was no evidence of fluctuation or abscess. Wasson[6] has shown that the antra are well developed at birth, but are not aerated, and require from four to eight weeks to aerate and become visible on the roentgenogram. In 3 of the 5 cases, aged four, five and six weeks, if we did not have the clinical evidence of a nasopharyngitis with pus in the nose, we could not assume that the opaque antra were diseased.

ROENTGEN THERAPY

Roentgen therapy has long been considered a very effective method of treatment for simple cervical adenitis and most radiologists have had experiences similar to Hurwitz and Zuckerman.[2] They report a carefully studied series of cases with controls showing that suppuration occurred in 14 per cent of cases treated with roentgen therapy in contrast to 41 per cent without roentgen therapy. Inasmuch as we[5] have had excellent results with roentgen therapy in chronic sinus disease in children, and finding sinus disease associated so frequently with retropharyngeal swelling, we have recommended small doses of roentgen radiation for all cases of retropharyngeal adenitis, and for all cases of retropharyngeal swelling where there is doubt as to the actual presence of fluctuation.

Of the 20 cases studied all but 3 were treated with roentgen therapy. One case, aged ten months, with a purulent bilateral otitis media and sinus disease, was treated with sulfanilimide and the glands promptly regressed as well as the otitis media and sinusitis. Two cases, aged eight and sixteen months, following a nasopharyngitis had small retropharyngeal glands which caused no obstructive symptoms, and were discovered only by roentgenographing the sinuses. The adenitis and sinus disease disappeared in three weeks following local treatment to the nose.

The remaining 17 cases were treated with roentgen therapy. Since the retropharyngeal adenitis was secondary to an infection in the sinuses or ears, the roentgen treatment was a slight modification of our routine roentgen therapy for sinus disease.[5]

Using 125 kv. (peak), 5 ma., 12 inch distance and 5 mm. aluminum filter, the daily dose is 75 r (measured in air) for infants up to one year, and 100 r (measured in air) from one to five years. One of three 15×15 cm. areas (right lateral, left lateral and anterior) is treated every other day until each area has been treated twice, or a total of six treatments in two weeks. Cases with considerable respiratory difficulty are usually given the two lateral treatments the first day, to hasten resolution. Large areas are used so that the sinuses, the mastoids, the retropharyngeal space and the entire upper respiratory tract is treated. The eyes are protected with small oval lead shields held in place with a band of adhesive tape across the nose. The hair is protected with lead. The uncooperative child is wrapped securely in a sheet, and the head is held by a nurse who wears heavy lead rubber gloves.

The retropharyngeal swelling disappeared entirely in all 17 cases following the roentgen therapy. The obstructive symptoms usually disappeared after the second treatment. The retropharyngeal swelling did not entirely disappear in any case under two weeks, and in 3 cases it was two

months before the retropharyngeal space returned to normal. We feel that the prompt resolution of the glands without going on to suppuration in any of the cases was due in part to treating the primary focus for the infection as well as the glands themselves.

CASE REPORTS

CASE I. Baby E. T., first seen on September 14, 1937, aged six weeks. The baby's delivery was normal and it was perfectly well during ten days' hospitalization. Two days after going home the baby began to cry a great deal and the mother noticed considerable nasal mucus. When fourteen days old the baby began having difficulty in nursing and since then had been unable to breath through its nose. After four weeks of age when the baby was placed over the mother's shoulder with the head partly flexed to regurgitate after feeding, the baby would struggle for air, turn blue and occasionally stop breathing. The baby would be fairly comfortable and breathing was slightly labored when lying on its back with its head flat. An enlarged thymus was suspected and the baby was sent in to the roentgen department for examination of the thymus. Roentgen examination showed the heart, thymus and lungs to be normal. The lateral view of the chest and nasopharynx during inspiration showed the retropharyngeal space to be greatly widened, measuring 15.0 mm. The nasopharynx was blocked. There was also a retrotracheal swelling with compression of the tracheal lumen so that it measured only 1.5 mm. (Fig. 1*A*). Examination of the sinuses showed the right antrum to be clear, the left was entirely opaque. Roentgen therapy was advised. Six treatments of 75 r were given and because of the pronounced symptoms, the baby was given 75 r to each lateral area the first day. Following the first day's treatment the baby began to breathe and nurse much easier. A checkup roentgenogram six days later (Fig. 1*B*) showed the retropharyngeal swelling to be less and the tracheal compression had disappeared. Two weeks after the first treatment the baby was having no symptoms, was breathing through his nose and had gained 14 ounces. The final roentgen checkup, six weeks after roentgen therapy (Fig. 1*C*) showed the nasopharynx to be normal and the baby has had no further respiratory difficulty.

CASE II. Baby D. J., aged two and a half, was first seen on April 17, 1936, complaining of an unexplained fever of three weeks' duration. His temperature would go to 102° F. each day, then following a sudden sweat would drop to normal. Two days before we saw the patient, he developed a small chain of right cervical glands. These glands were given two roentgen treatments of 100 r in three days. The glands promptly disappeared and the temperature remained normal for seven days, when the glands and fever returned. Sinus disease was suspected as the focus for the infection and roentgenograms showed the ethmoid sinuses to be clouded and the antra showed marked

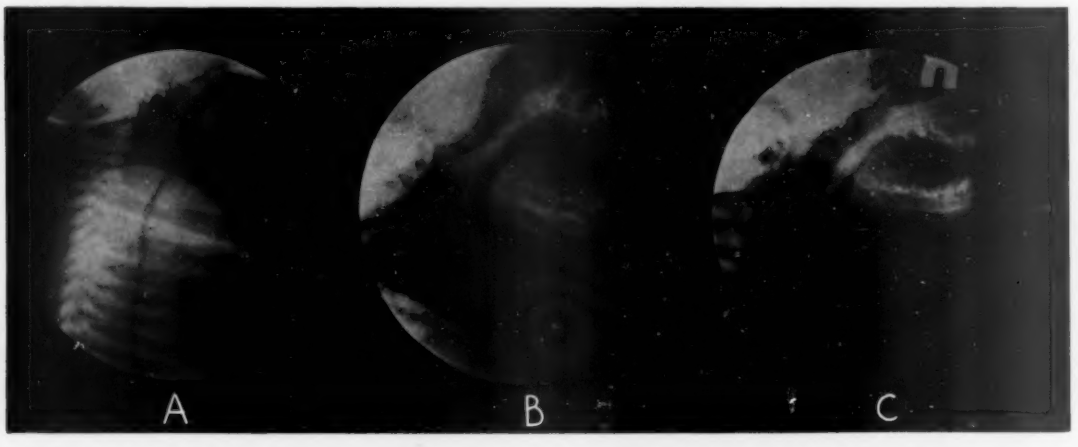

FIG. 1. Case I. *A*, the pronounced retropharyngeal and retrotracheal swelling produces almost complete tracheal compression in a six weeks' old infant. *B*, six days after beginning roentgen therapy the swelling is regressing and the tracheal compression has disappeared. *C*, six weeks after therapy the retropharyngeal space is normal.

Fig. 2. Case 11. *A*, moderate retropharyngeal adenitis, associated with cervical adenitis and sinusitis. *B*, one month after roentgen therapy the retropharyngeal space is normal.

thickening of the mucosa. The lateral view of the nasopharynx showed a moderate retropharyngeal swelling which produced no symptoms (Fig. 2*A*). The patient was given two treatments of 150 r to a large area over the sinuses and pharynx. The large recurrent cervical glands softened, suppurated and were incised and drained. The patient improved immediately. Checkup roentgenogram of the sinuses one month later showed the retropharyngeal space to be normal and the sinuses entirely clear (Fig. 2*B*).

SUMMARY

1. The normal retropharyngeal space during inspiration in infants and children should not measure over 11 mm. using ordinary roentgenographic distances.

2. A retropharyngeal swelling is usually due to some focal infection in the upper respiratory tract, often the nasal accessory sinuses.

3. If both the focal infection and the retropharyngeal swelling, usually an adenitis in the early stages, are treated promptly with roentgen therapy, a retropharyngeal abscess rarely develops.

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ROENTGEN DIAGNOSIS OF DERMOID CYSTS OF THE OVARY IN THE ABSENCE OF CALCIFICATION*

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THE roentgen diagnosis of dermoid cysts of the ovary[1–13] is usually based on the presence of teeth or other calcified shadows; the latter may be either amorphous agglomerations or the true osseous formations.[3] In many instances the discovery of these tumors is made fortuitously in the course of roentgen studies which include the pelvic abdomen. The incidence of calcification in dermoid cysts is reported in two pathological studies[5,8] as varying between 18 and 49 per cent. Since dermoid cysts constitute nearly 20 per cent of all ovarian tumors, it would be desirable to have additional reliable roentgen diagnostic criteria to make possible the detection of the large number of these tumors which do not contain calcareous material.

In the following 6 instances, representative of a group of 22 cases, the roentgen diagnosis of dermoid cyst of the ovary was made on the basis of signs which we believe are constant features of these tumors and which do not depend on the presence of calcified material. A rounded or ovoid mass of decreased density, regular in its contour, is found in the pelvis; it usually presents a banded, mottled appearance. This mass is sharply delineated from the surrounding soft tissues by a thin ring of increased density. Repeated examinations of the same region will always present a similar picture, so that the constancy of these features represents confirmatory evidence.

CASE REPORTS

CASE I. (Fig. 1*A*.) J. F., aged twenty-nine. Uterosalpingography was performed because of a complaint of sterility; the films showed the uterus to be normal. On the left side of the pelvis, in the region of the ovary, a small, rounded area of diminished density was noted. This area was sharply circumscribed by a dense ring shadow, and the mass presented a slightly mottled appearance. The film taken after the lipiodol emptied from the uterus (Fig. 1*B*) showed the same appearance. The diagnosis of dermoid cyst of the ovary was confirmed at operation.

CASE II. M. H., aged twenty-six. A flat plate of the abdomen, taken for gastrointestinal complaints, revealed in the pelvis a large round mass, measuring about 14 cm. in diameter. The mass presented a banded, mottled appearance and was encircled by a dense ring shadow. No calcified foci could be demonstrated (Fig. 2). On the basis of these features, a diagnosis of dermoid cyst was made and later confirmed at operation. Pathological examination showed no evidence of calcareous material.

CASE III. B. M., aged twenty-three. Studies for urinary complaints included a flat film of the pelvic region and demonstrated a small, irregular calcified shadow in the pelvic region. This shadow, however, was noted to lie within an area of decreased density which was slightly mottled in appearance and encircled by a well defined ring of greater density (Fig. 3). In view of these findings, it was felt that the calcified body represented an imperfect tooth formation within a dermoid cyst. The diagnosis was proved to be correct at operation. This case demonstrates an example where the aforementioned characteristics peculiar to dermoid cyst aided in the differential diagnosis of a calcified shadow in the pelvis.

CASE IV. B. G., aged seventy. Roentgen studies of the lumbar spine were made because

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FIG. 1. *A*, note the relation of the mass to the lipiodol-filled uterus; the latter appears to be normal. The diminished density of the mass is well illustrated. *B*, the small scattered dense areas are due to small amounts of lipiodol in the pelvis which have gone through the Fallopian tubes. A small residue of lipiodol may also be present within the uterus.

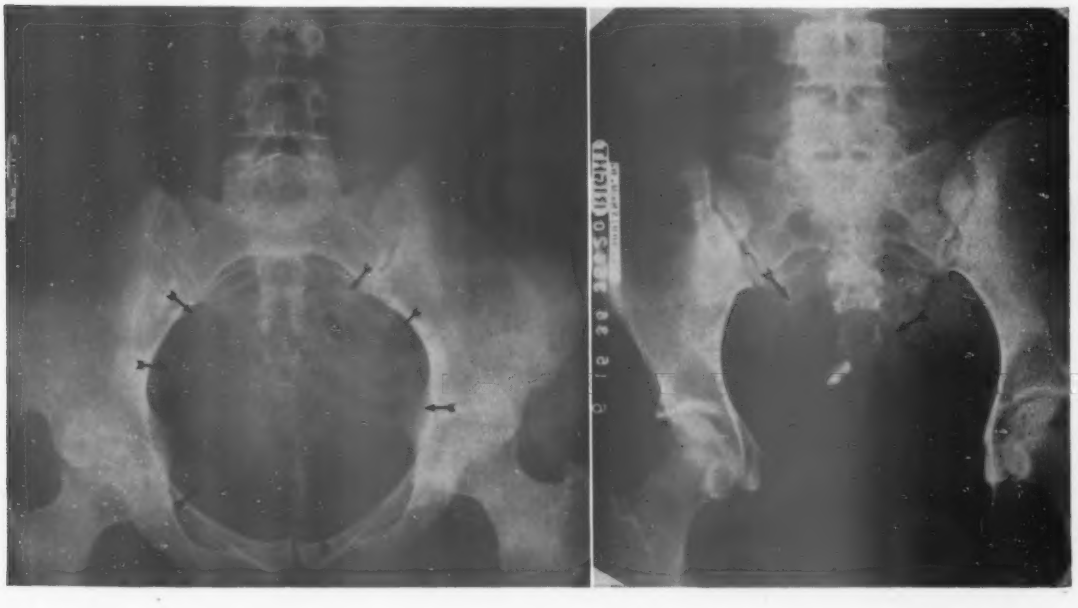

FIG. 2 (*left*). The encircling ring of the cyst is well defined at the inferior and lateral borders of the mass. This cyst measured 14×11.5×9.5 cm. and contained hair and sebaceous material.

FIG. 3 (*right*). The calcified area is poorly differentiated, but was identified as a tooth on pathological examination.

of low back pain. A large, rounded mass was noted in the pelvis; its general appearance was similar to that of the dermoid cysts described above. The marked degree of mottling was an outstanding feature in this particular instance. An irregular, calcified area was noted in the

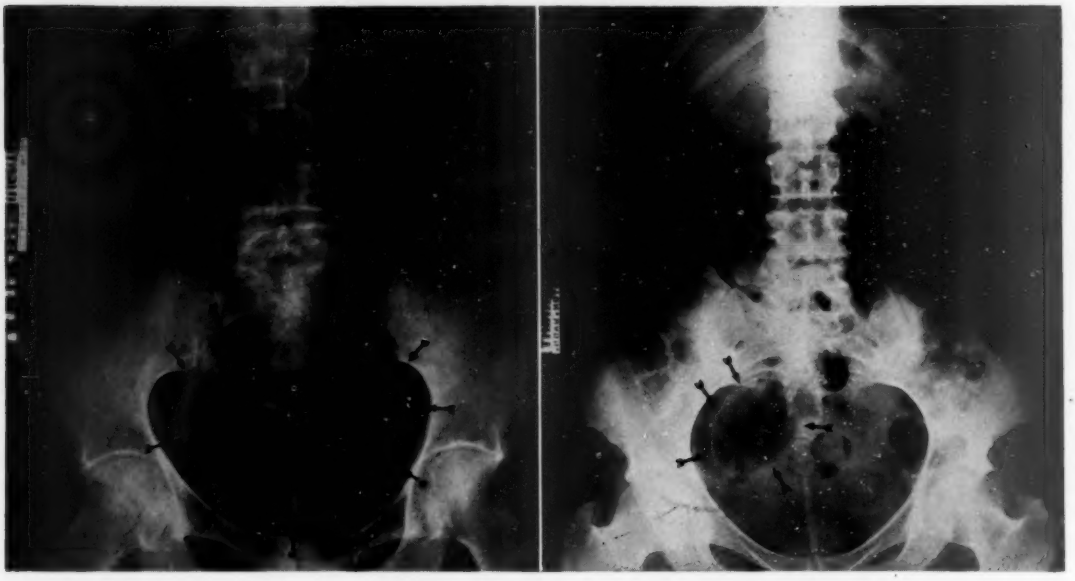

FIG. 4 (*left*). Note the marked degree of mottling. The small calcified shadow just above the mid-point of the pubis probably represents an incomplete tooth formation. The sharp demarcating ring adds to the contrast to the surrounding soft tissues.

FIG. 5 (*right*). The ovoid area of increased radiance is well outlined. The dense wall surrounding the area is sharply defined and is characteristic of a dermoid cyst.

FIG. 6. *A*, the ureteral calculus is about the same size as the calcified bodies within the cyst. An irregular calcified plaque is present in the superior portion of the cyst wall. *B*, the calculus has been passed. Note the contrast to the intestinal shadows on the other side of the pelvis.

inferior portion of the cyst, probably representing a tooth formation. The whole area was confined within a contrasting ring of increased density (Fig. 4). A roentgen diagnosis of dermoid cyst was made. Operation was deferred because of the extreme age of the patient.

Case v. (Fig. 5) A. W., aged thirty-nine. This patient was referred for urologic studies, at which time a film revealed, in the vicinity of the right ovary, an ovoid area of decreased density. This area stood out in contrast to the surrounding denser tissues and this contrast was made more marked by an encircling ring of increased density. The contents of the rounded area showed a mottled appearance. Two later examinations showed the same features noted at the first examination. These constant findings warranted a diagnosis of dermoid cyst. No operation was performed.

Case vi. S. S., aged fifty-four. The history included right-sided abdominal pain, frequency and dysuria. At the first examination (Fig. 6*A*) a small, right ureteral calculus was noted. Just above the calculus and in the region of the right ovary was a rounded area of decreased density, banded and mottled in appearance, and encircled by a dense ring shadow. Small foci of irregular calcifications were noted within the mass. In addition, part of the wall showed a relatively denser area, suggesting a plaque of calcification. A diagnosis of right ureteral calculus and right ovarian dermoid cyst was made.

The ureteral stone was passed and a second roentgenogram (Fig. 6*B*), taken two months later, showed no evidence of any calculi. The rounded area in the region of the right ovary persisted, similar in size, shape and appearance to the mass noted at the previous examination. In view of the constant findings, it was felt that a diagnosis of dermoid cyst was warranted. A third film, taken a year later, showed no change in size or appearance of the cyst.

This case demonstrates the fact that repeated examinations in the presence of suspected dermoid cyst of the ovary shows constant findings which differentiate a cyst from confusing shadows due to intestinal gas.

DISCUSSION

Films of the pelvic abdomen in the 6 above-described cases showed masses which, except for size, resembled each other closely in appearance. The mass was always found in the pelvis and usually in the vicinity of one of the ovaries. If the cyst was large, it occupied the greater portion of the pelvis, as in Cases ii and iv. The diminished density of the mass is explained by the nature of the contents of the dermoid cyst, a sebaceous material which is liquid at body temperature. Dermoid cysts all contain varying quantities of hair mixed with the sebaceous material; this accounts for the banded, mottled appearance so characteristic of these ovarian tumors. Case iv shows the mottling especially well. All the cases show a definite capsular ring of increased density; this is explained by the capsular structure of the dermoid cyst which is made up of thickened stratified squamous epithelium and supporting fibrous tissue. An occasional plaque of calcium is noted in the wall, as in Case vi.

These characteristics, in the absence of calcification, have been sufficient to make a roentgen diagnosis of dermoid cyst and have also aided in the differential diagnosis of calcified shadows of doubtful origin in the pelvis. This is illustrated in Case vi where both a ureteral calculus and calcified parts of the dermoid cyst were present. After the passage of the calculus, the remaining calcified shadows were easily identified as cyst contents. The criteria described above should also facilitate the differential diagnosis of dermoid cysts in the presence of vesical calculi, phleboliths, calcification in the ovary, calcified fibroids, calcified glands, and healed tuberculous salpingitis with calcification.

SUMMARY

Criteria for the roentgen diagnosis of dermoid cysts of the ovary are presented which make the diagnosis possible in the absence of formed calcified shadows. A rounded or ovoid mass of diminished density, banded and mottled in appearance, is noted in the pelvis. The mass is encircled by a well defined ring of increased density, sharply delineating the mass from the surrounding soft tissues. These roentgen features of the dermoid cyst are also useful in differential diagnosis when a calcification in a dermoid must be differentiated from other calcified shadows in the pelvis, such as ureteral and vesical calculi, phleboliths,

calcification in the ovary, calcified fibroids, calcified glands and healed tuberculous salpingitis with calcification.

Six cases are presented to illustrate the roentgen diagnosis of dermoid cyst of the ovary; in three of them the diagnosis was confirmed by operation.

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CALCIFICATION OF THE PERICARDIUM*

REPORT OF A CASE IN A BOY AGED TWELVE

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WHILE calcification of the pericardium is a common post-mortem finding, the clinical diagnosis presents many difficulties. Few cases have been diagnosed during the lifetime of the patient and these always by roentgenographic methods. A survey of the recorded instances of patients presenting definite evidence of calcification of the pericardium will show that they are mostly from higher age groups. Consequently, the following case seemed to us worthy of recording on account of the youth of the patient and the marked degree of the process.

REPORT OF CASE

R. F. (No. 449) was first seen on January 27, 1934, at age of nine and a half. The chief complaint at this time was cyanosis on slight exertion of a year's duration. When first noted by the mother of the patient the cyanosis appeared only when running or when entering cold water at the seashore. When patient consulted the family physician for cough at this time cardiac enlargement was first noted. A few weeks later swelling of the abdomen appeared and the patient was tapped for the first time a month before this examination. No edema of the feet. Slight dyspnea on moderate exertion.

Past Medical History. Negative for rheumatic infection of any type. Measles, whooping cough and chickenpox in infancy. Rickets diagnosed at age of eight months. At age of four patient had abscess of right ear with uneventful recovery. The tonsils were removed later the same year.

Social History. Attends school (4B). Born New York City and always lived there. Birth a version and labor long and hard. No cyanosis at birth. Walked at sixteen months. Talked at eighteen months.

Family History. Mother and father living and well. Three siblings, all living and well. The maternal grandmother had diabetes. The maternal grandfather had tuberculosis. The paternal grandfather had hypertensive cardiovascular disease. No history in family of rheumatic infection.

Physical examination at this time showed no appreciable increase in cardiac size. A blowing systolic murmur was heard transmitted to axilla. The abdomen was large and the liver was palpable a hand's breadth below the costal margin. Free fluid was demonstrated in the abdominal cavity.

An electrocardiogram was made at the time patient was first seen (Fig. 1*A*). The blood count: red blood cells 3,970,000, hb 69 per cent. Differential normal. Wassermann and Kahn tests normal. Blood urea 10 mg. per 100 cc. Glucose tolerance normal. Blood sugar 100 mg. per 100 cc.

The patient was advised to enter the hospital to confirm tentative diagnosis of Pick's disease but was not seen until May 4, 1936, when he was admitted to the service of Dr. E. Bacon at the Woman's College Hospital. At this time chief complaints were fluid in abdomen for three years, edema of legs for nine months and edema of face for three months.

The patient had obviously lost ground since last seen. No further growth was noted, the abdomen was tightly distended with fluid, the face and legs were edematous, cyanosis was present and a moderate degree of dyspnea was present on slight exertion. He had been tapped at least once a month since last seen but on each occasion the abdomen filled again very quickly. He stopped school ten days ago and bed rest improved his condition slightly.

Examination showed edema of the face more marked on the right side. The teeth, nose and throat were negative. The anterior cervical glands were slightly enlarged. The jugular veins were quite prominent on both sides. The anteroposterior diameter of the thorax was unusually wide. The chest was barrel shaped with flaring of the lower ribs. No left-sided precordial bulging was seen. There was no retraction of interspaces. More expansion was felt to occur in anteroposterior direction than laterally on deep inspiration. There was no tracheal deviation.

* Read before the Philadelphia Roentgen Ray Society, November 4, 1938.

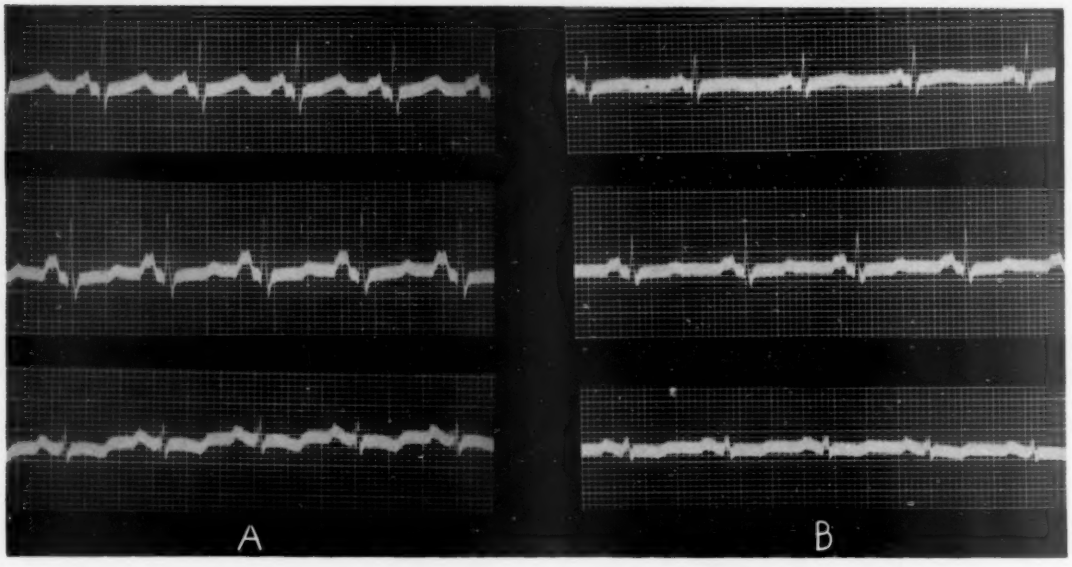

FIG. 1. *A*, January 27, 1934; *B*, May 5, 1936.

Abdomen distended. Fluid readily demonstrated. No distention of superficial veins was seen. No inguinal adenopathy. The liver was enlarged and smooth and the edge could be made out 9.5 cm. below the costal margin. Spleen not palpable. No other masses felt.

Cardiac Examination. Blood pressure: right arm, 94/62; left arm, 88/64. Apex beat palpated in the 4th intercostal space about 1 cm. to left of the mid-clavicular line. It did not move on change of position. The heart sounds were of good quality, rhythm regular, rate 86. The aortic second sound slightly louder than the pulmonic second sound. There was a systolic murmur heard over the apex and a faint mid-diastolic murmur in the same region. No thrill was palpable over any valve area.

Extremities were normally developed. All reflexes normal. Slight pretibial edema present.

A second electrocardiogram was made (Fig. 1*B*). A decided decrease in voltage was noted when compared to previous examination. Notching of the P-waves, particularly in lead 2, is seen together with changes in the T-waves. No axis deviation was demonstrated with change in position.

Roentgen examination of the chest (Figs. 2 and 3) showed a circle of calcium in the pericardium. Diminished amplitude of the cardiac impulse was seen on roentgenoscopy. The heart was slightly above upper limits in size. The cardiothoracic ratio measured 0.48. There was fullness in the region of the left auricle. The supracardiac shadow was wider than usual, either due to dilated vessels, enlarged lymph nodes or effusion between the lung and mediastinum on the right—probably the latter. There was some pleural thickening over both lungs with a moderate pleural effusion of the right side.

A roentgenogram of the abdomen showed a moderately enlarged liver, the measurements from the right border to the dome of the right diaphragm being 19 cm. This was about 5 cm. above the upper limits of normal. The spleen was slightly enlarged. The kidneys were within normal limits in size, smooth in outline and occupied normal positions. There were no abnormal calcifications within the abdomen. The abdominal wall was slightly thicker than usually compatible with thickening of the peritoneum.

Roentgenograms of the long bones showed no evidence of bone or epiphyseal changes.

Impression: Findings compatible with clinical diagnosis of polyserositis. Calcification in the pericardium marked.

Examination of the urine was normal on three occasions. The blood count showed improvement since the last examination: red blood cells 4,250,000, hb 86.6 per cent (Sahli), white blood cells 7,800. Differential: neutrophiles, 72 per cent; lymphocytes, 19 per cent; monocytes, 6 per cent; eosinophiles, 3 per cent. Sedimentation time: 18 mm. in seven hours. Icteric index, 10; hemolysis, 0.40 to 0.28 per cent.

Blood Chemistry. Urea nitrogen 11 mg. per

100 cc., cholesterol 90, phosphorus, 2.44, calcium 7.9, glucose 69.5. Urea clearance normal. Ascitic fluid: total chlorides 630 mg. Albumin three plus. Culture of ascitic fluid, no growth. Mosenthal, normal range of figures.

Clinical Diagnosis. (1) Etiological, unknown; (2) anatomical, slight cardiac enlargement, mitral regurgitation, pericardial adhesions with calcification of the pericardium; (3) physiological, normal sinus rhythm; (4) functional classification, Class 2b (faulty diastolic filling).

The patient appeared to be declining very fast. The jugular veins were more distended and the abdomen filled quickly after each weekly tapping. The procedure caused the patient much discomfort and considerable apprehension. There was continued venous hypertension following abdominal tap, the readings averaging 190 mm. The situation was explained to the parents and pericardiectomy advised.

The child was moved to the Mayo Clinic and operated on the following week. The following note received from Dr. Samuel Amberg describes the findings:

The pericardium was found to be adherent to the heart throughout its entire extent and a layer of calcium was present throughout its entire attachment, the deposit being most marked along the diaphragmatic portion of the pericardium and about the inferior vena cava. On the other areas it was granular and piled up in character. The entire pericardium was separated from the heart muscle, the left ventricle freed first and the calcium removed from around the pericardium and vena cava orifice. About two-thirds of the pericardium was removed entirely freeing the vena cava and heart muscle. It was a very difficult and extensive procedure because of the firm attachment of the calcium to the pericardial layers. In fact, some of the calcium had to be left attached to the auricle and inferior vena cava. Considering the magnitude of the operation the patient stood the actual procedure very well. During the night following the operation the patient showed good response. During the second day there was a gradually increasing respiratory difficulty with a steady fall in blood pressure. In spite of the usual supporting measures, oxygen and transfusions, the patient died on the morning of the third postoperative day. No autopsy was obtained.

DISCUSSION

Although Morgagni[1] is usually credited with the publication of the first case report of pericardial calcification in 1762, Dionis[2] gave a clear description of the condition in 1705. In 1768 Bordenave[3] reported a case showing calcification of the pericardium to the extent of an inch in a patient of fifty, who died of congestive cardiac failure. The first case report containing an illustration of the condition appeared in 1783 and was given by Simmons and Watson.[4] Here the finding of the pericardial calcification was

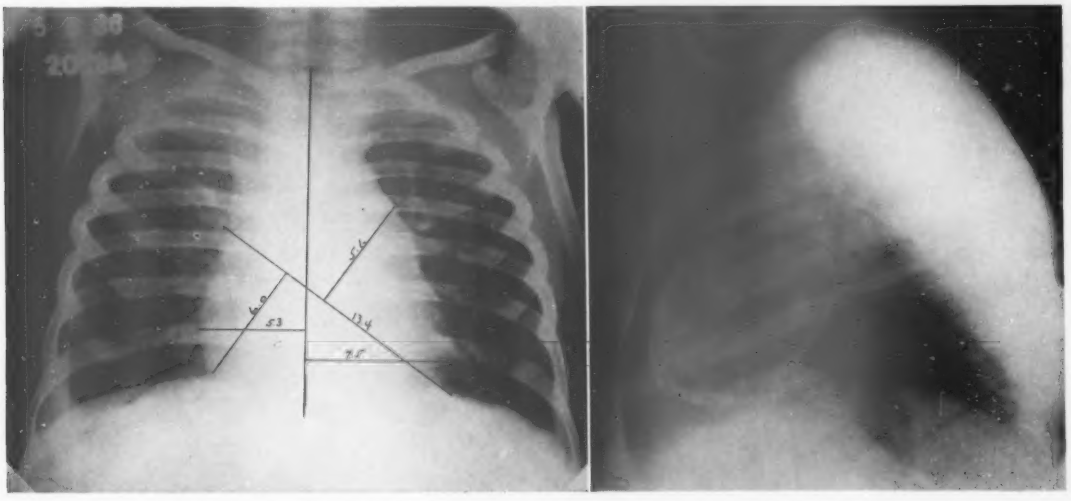

Fig. 2 (*left*). Posteroanterior roentgenogram of chest. There is an increase in diameter of the base of the heart but no increase in the transverse diameter. There is increase in the transverse diameter of the supracardiac shadow due to dilated superior vena cava. There are congested pulmonary vessels, with pleural thickening and effusion. Calcification not discernible with the usual exposure in this projection.

Fig. 3 (*right*). Lateral projection of the chest of the same patient as in Figure 2. Note extensive calcification at periphery of cardiac silhouette. There is an increase in the anteroposterior diameter of the chest.

entirely accidental, the patient dying of carcinoma of the esophagus and no symptoms of heart disease were recorded during life. Watson suggests, "the measure of every morbid ossification will no doubt depend much on the abundance of creta in the habit. That it does abound in some and that it is very deficient in other constitutions we are fully convinced . . ." In 1809 Burns[5] for the first time reported a patient with a heart " . . . diseased with specks of bone . . . ," and in 1849 Rokitansky demonstrated a case of apical calcification and described the microscopic appearance of calcium granules deposited between the necrotic muscle fibers. It was not until 1910 that Schwartz reported a case of pericardial calcification recognized for the first time during the life of the patient. This was done using the roentgenologic method.

Calcification of the pericardium, if we are to judge from the number of cases reported in the literature, is a rare lesion. Turner,[6] searching the literature in 1924, reports 89 cases and adds 3 of his own. Smith and Willius[7] in 1932 reported 15 cases in which presence of calcification was diagnosed during life and proved at necropsy. In their series the youngest subject was twenty-four years of age and the oldest eighty-four. The average age of the series was 48.6 years.[8]

ETIOLOGY

In the reported cases no general agreement exists in regard to the etiology in calcification of the pericardium. Most cases are first encountered at autopsy and the etiological factor remains obscure because evidences of the original infection cannot be determined with accuracy. The pathological identification markings are buried in the obscurity of the fibrous tissue and calcium. Few cases have been followed with accurate records from the acute stage to the stage of calcification to establish a cause and effect relationship. Youmans[9] and Youmans and Merrill,[10] in a study of 3 cases of their own and after reviewing the histories of collected cases, favor tuberculosis as the commonest etiologic agent in most instances. However, Bellet and McMillan,[11] in a study of 100 cases of tuberculosis of the pericardium at the Philadelphia General Hospital, did not find calcification in a single instance. Smith and Willius[7] did not find any evidence of tuberculosis in their series of cases. The single etiological factor that affected the largest number of cases in their group was rheumatism. A few cases undoubtedly are of this origin. It is likewise true that many previously undiagnosed inflammations about the pericardium at the time of an influenzal or pneumococcic infection are the starting points of the process that later receives the deposits of calcium. Rarely is syphilis the cause. Of all the etiological agents mentioned above, the pneumococcus is the most likely one to leave behind the proper soil for the development of calcification. The pericardium lies in contact with the mediastinal structures and an inflammatory process arising in the course of an influenzal, pneumococcic, rheumatic or streptococcic infection can easily spread with initial involvement of all these important structures. The etiological agent in scarlet fever is closely allied to the organism responsible for the rheumatic state and it is not unlikely that inflammatory changes occur in the course of scarlet fever and result in the production of necrotic tissue soil for the deposit of calcium.

A number of factors have been claimed to influence the deposit of calcium salts in the pericardial tissues. The best soil is prepared by a mass of necrotic tissue in this locality that receives a poor blood supply. A local increase in the alkalinity of the blood at times renders the calcium salts less soluble and more likely to deposit. This will occur more often in individuals who have an overloading of the blood with calcium and phosphate salts. Factors that act from time to time to cause concentration of the blood under these favorable conditions may assume the rôle of immediate causes. The vitamins and the hormone

of the parathyroid glands have likewise been mentioned as agents in the process.

Sex is a factor. In all the series reported in the literature males are more often affected than females in the ratio of 3:1.

Regardless of the etiological factor, the inflammatory process involving pericardium and mediastinal structures may burn itself out with the formation of some fibrous adhesions between the layers of the pericardium, in which event little harm results. If, however, as in this case, calcium appears early and is deposited all over the pericardial surface, symptoms of a cardiac nature are soon seen. The amount, degree and location of the calcium and its association with adherent pericarditis are the important points. The heart in this patient produced symptoms when it sought to attain its normal growth in a restricted space. If there is a valvular lesion in addition, the embarrassment will occur sooner. Firm attachment of the heart to surrounding structures by extrapericardial adhesions may complicate the picture still further by limiting cardiac contraction. Operation on this patient showed that the calcium deposits about the orifices of the superior and inferior vena cavae were the main factors in influencing the clinical course. The encroachment on the lumen of these vessels gives rise to certain recognizable syndromes. With involvement of the superior vena cava the obstruction to the return flow of blood from the face and neck causes edema in these regions. Evidence of the increased venous pressure in this part of the body is seen in the engorgement of the veins of the neck and cyanosis. The venous pressure readings in this boy were always markedly elevated. If the flow is obstructed in the pulmonary artery, pulmonary hypertension and right ventricular strain result. In obstruction of the inferior vena cava we note enlargement of the liver to a much greater size than is usually found in cases of congestive cardiac failure, ascites, edema of the legs and hydrothorax. These are out of proportion to signs of involvement in the lesser circulation. Low blood pressure is a common finding and nearly always a low pulse pressure.

CLINICAL DIAGNOSIS

In most cases the presence of the signs above described lead to an initial diagnosis of progressive cardiac failure. However, suspicion should be aroused when the heart size is much below the expected picture. The finding of cyanosis is another important point in the diagnosis that should lead to a thorough roentgen study. An early, correct diagnosis of calcification of the pericardium is extremely important, for if the signs presented are attributed to other factors it will prevent the consideration of operative relief now proved to be of outstanding value in the treatment of these cases. The formation of the chest in this case was significant for we do not find a barrel-shaped thorax in one so young without good reason. In this patient there was more expansion in the anteroposterior plane than laterally. The apex beat was fixed but no retraction of the ribs and interspaces was noted. Today, when roentgenoscopy in these cases is usually first carried out by the internist, the discovery of the "small, quiet heart" may give the first clue and the presence of calcification demonstrated on subsequent plates may determine the diagnosis.

The electrocardiogram in the patient reported here is interesting (Fig. 1). Comparing the one taken on January 27, 1934, with the one obtained on last admission a striking change will be seen. The first tracing is normal with the exception of P-wave notching and a slight depression of the S–T intervals in lead 2. In the last tracing the difference in the amplitude or voltage of the QRS groups and the flat T-waves should be noted. This change is not an infrequent finding in cases of calcification of the pericardium particularly after the development of extensive anasarca.

Reviewing the auscultatory findings in the case reported here we note that a murmur was heard over the region of the apex

in mid-diastole. There was considerable discussion at the time over the interpretation of this extra sound thought by some to be a murmur significant of a stenotic lesion of the mitral valve and by others to be an unexplained extra sound in the middle of diastole. Considering the marked alterations in the tissue structure and the increased density of the calcified pericardium an extra sound in diastole would seem to be a reasonable finding. However, it was not until reading the recent article by Lian, Marchal and Pautrat[12] that the significance of the sound we heard over the apex in diastole in this patient became clearly understood. These authors describe a sound protodiastolic in time in 2 cases of calcification of the pericardium that is louder at times than the heart sound giving a gallop rhythm best heard between region of the apex and end of sternum. This extra sound (described as a vibrance) should always lead the clinician to make a thorough study for the presence of calcification. It has a peculiar vibration that other sounds, occurring at this time in the cardiac cycle, do not have and this quality serves to distinguish it. The physiological reduplication of the second heart sound is best heard over the base. The physiological third heart sound does not have the intensity nor the vibration that this extra sound possesses. The mid-diastolic mitral stenotic murmur is not accentuated nor as loud as this vibrance but, as in this case, mitral stenosis is often suspected because it is the commoner lesion. Roentgen examination serves to make the differentiation. In the case of mitral stenosis, there is mitralization of the left cardiac border and if the sound arises from this type of pericardial involvement, we see the calcium. Bouillaud may have heard this sound for he speaks of a case of a myocardial stony projection into the pericardium giving a scraping sound but he does not describe it further nor does he mention the time in the cardiac cycle.

However, in many cases the different signs and symptoms that we have described may prove inconclusive. The main diagnosis then rests upon the roentgen findings.

ROENTGENOLOGICAL ASPECTS

A good roentgenologist must first be a good clinician. In the presence of any or all of the above manifestations, chronic adhesive pericarditis with calcified pericardium should be suspected and the following roentgenologic evidence sought:

1. Absence of cardiac pulsations or diminished amplitude of pulsation.
2. Slight cardiac enlargement with disproportion between the degree of circulatory embarrassment and the size of the heart.
3. Irregularity and haziness of the cardiac silhouette due to external adhesions uniting the pericardium to the pleura, adjacent mediastinal tissues, thoracic wall or the diaphragm.
4. Inability of the heart to change its position during the various phases of respiration.
5. Increase in the transverse diameter of the supracardiac shadow, due to stasis in the venous circulation, with dilatation of the veins.
6. Presence of calcification in the pericardium.
7. Characteristic kymographic changes.
8. Fixation of the dome of the left diaphragm.
9. Elevation of the diaphragm and limitation of the respiratory excursion with small pleural effusion.
10. Increase in the lung markings due to congested pulmonary vessels with stasis in the lesser as well as the greater circulation.

The cardiac measurements in our case were 5.3 cm. from midline to right border, 7.5 cm. from midline to left border; the cardiothoracic ratio was 0.48, the length of the heart was 13.4 cm., and the diameter at the base was 11.6 cm. These two measurements, particularly the diameter at the base, are definitely above the upper limits of normal.

The case reported by us in this communication showed the above changes. It should be noted that the calcification can only be seen in the oblique projection and not in the anteroposterior projection.

It is important to make a differential diagnosis from the film between calcified pericardium and calcification of the heart muscle or endocardium. Calcification of the heart muscle is usually seen in older individuals. This type of calcification is not at the periphery, it involves smaller areas and is not associated with such absence or such marked diminution of the cardiac impulse as occurs in calcification of the pericardium.

TREATMENT

The only treatment is surgical. Success follows early diagnosis, good preparation of the patient and the selection of an experienced surgeon. The procedure is the removal of the mechanical impediment to the circulation and there are several types of operation.

Brauer[13] in 1902 first suggested subperiosteal resection of the left fourth, fifth and sixth ribs with their cartilages, extending from the mid-clavicular line or beyond to the sternum. This procedure allows greater freedom of movement for the heart and does not involve a great risk. Properly carried out it is attended with little shock and the relief obtained warrants more common employment in these cases.

Another type of operative procedure called for in the case reported here is the removal of portions of the pericardium from the heart itself, particularly the ventricle. At the same time the layer of calcium is removed from around the orifice of the inferior vena cava. Results achieved by this type of surgery are the most brilliant in medicine. A number of striking cases of relief and cure have been reported by White,[14] Churchill,[15] Beck and Griswold,[16] and Flick and Gibbon.[17] Improving surgical techniques and closer cooperation between internist, roentgenologist and surgeon in the handling of these patients point to an even more promising future for this field.

SUMMARY

1. A case is presented in detail of a boy, aged twelve, who showed a combination of calcification and adherent pericardium resulting in Pick's syndrome with pleural effusion, ascites, large liver and edema of the extremities. In this patient operative relief was attempted.

2. A discussion of the incidence, etiology, clinical and roentgen diagnosis of calcification of the pericardium is given. Early diagnosis and the benefit of surgical treatment are emphasized.

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SILICOSIS AND TUBERCULOSIS ROENTGENOLOGICALLY SIMULATING A NEOPLASM

REPORT OF A CASE

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SILICOSIS usually produces a fairly typical picture in the roentgenogram, the lesions being seen in the periphery of the lungs. The differential diagnosis can be made as a rule on the basis of exposure of the individual to dust. The case here reported is quite exceptional in that the roentgen findings were very suggestive of a neoplasm while the autopsy revealed only hilar silicosis and tuberculosis. Furthermore, it was impossible to find a source of silica.

CASE REPORT

A white male, aged thirty-six, was admitted to the State of Wisconsin General Hospital on November 26, 1937, with the complaint of shortness of breath, which was especially marked upon any physical activity. Before coming to Wisconsin he had had a radical antrum operation in Texas without relief of his symptoms. The pertinent findings upon physical examination were some weight loss, a few pulmonary râles and a prolongation of the inspiratory and expiratory note upon auscultation. In addition he had a tachycardia.

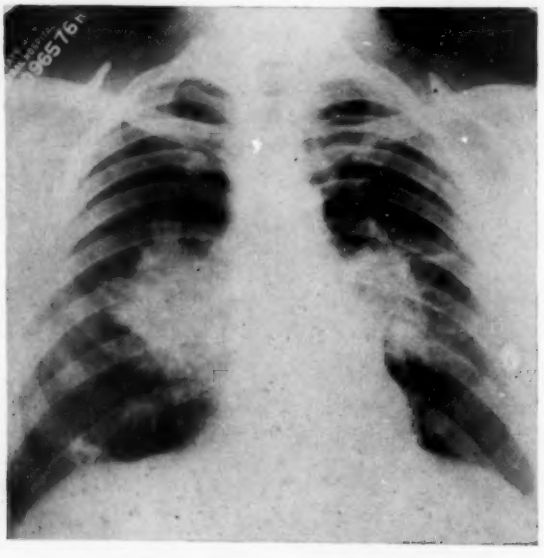

FIG. 1. Roentgenogram taken November 27, 1937, in Madison.

Roentgenograms of the chest showed a large irregular mass projecting from the right mediastinum into the lower lungs, and a similar smaller mass with fuzzy edges was seen projecting on the left side (Fig. 1). There was a little shrinkage of the left upper lobe with thickening of its interlobar pleura. The lungs were elsewhere clear. The bizarre findings in the chest were very strongly suggestive of a primary bronchogenic carcinoma with bilateral lymphatic spread. Roentgen examination of the sinuses showed an opaque maxillary antrum, the remaining sinuses being clear.

Bronchoscopic examination was done; it revealed some stenosis below the bifurcation of the major bronchi on the right side, apparently due to some pressure from without rather than from a growth within the bronchial tree. Since surgical removal seemed to be impossible it was decided to give roentgen therapy a trial. From December 2 until December 17, 1937, he received, as an outpatient, a total of fourteen exposures over the anterior and posterior mediastinum, 200 r (in air) per field, half-value layer of copper 1.35 mm. The skin erythema had developed by the time of the last treatment, and the patient was asked to return for re-examination within three weeks. However, he insisted on returning to Texas and in order to permit a proper follow-up, he was referred to a radiologist near his home town for examination and treatment if indicated.

On January 26, 1938, he was admitted to the local hospital in Texas with a temperature of 102.6° F. and a pulse rate of 112. Roentgen examination showed no appreciable change of the process in either hilar region but there was considerable infiltration at the right base, and the left upper lobe looked more cloudy (Fig. 2). Four additional treatments were then

given through left and right oblique fields in order to avoid the previous portals of entry which still showed marked pigmentation. The patient began spitting up some purulent material and seemed to be steadily declining. He desired then to return to Madison and was placed on the train. He died en route and a partial post-mortem examination was made in Oklahoma. At that time most of the right lung and heart were removed and placed in a glass container to be sent here for further study. The examiner in Oklahoma did not find sufficient pathology to cause death. Our own post-mortem findings follow:

Autopsy Report. The body had been embalmed, and a partial autopsy had already

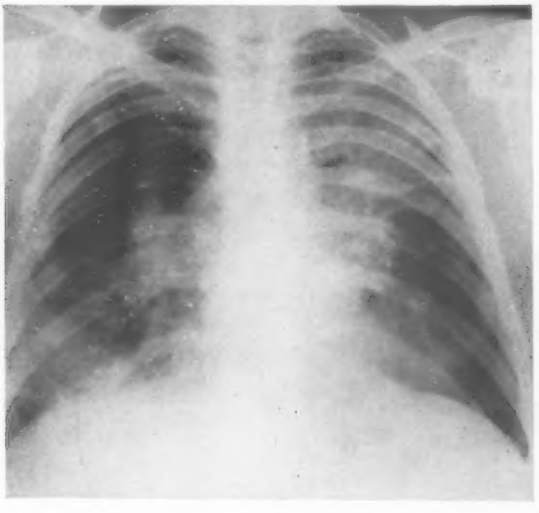

Fig. 2. Roentgenogram taken on January 29, 1938, in Texas.

been performed as described above. *Lungs:* The two lungs were essentially similar, and so will be described together. The pleura was smooth and glistening, and no adhesions or fibrous tags could be found. The hilar portion was very dense and fibrous; this fibrous area involved about one-third of the volume of each lung, and was irregular in shape. The bronchi running through the dense area were thick-walled and had evidently been compressed by the contraction of the surrounding fibrous tissue. The peripheral portions of the lungs were air-containing, although the framework was somewhat thickened. Carbon pigment was present throughout, but was especially dense in the hilar fibrous portion.

Microscopically, the lesion at the hilum was

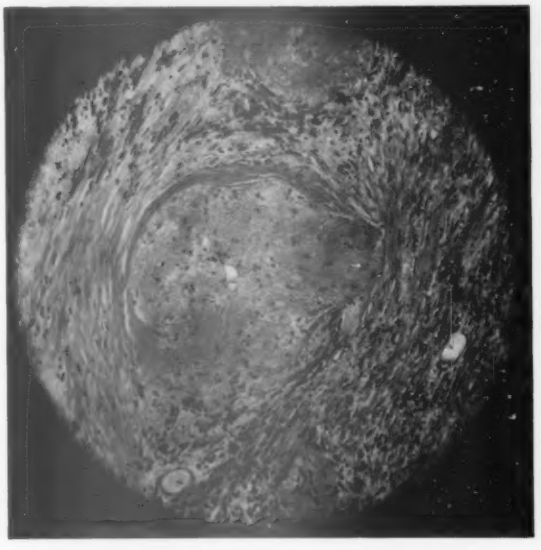

Fig. 3. Silicotic nodule.

composed of very dense fibrous tissue nodules, chiefly perivascular in distribution, but coalescing to form a dense mass (Fig. 3). A few tubercles containing giant cells were seen (Fig. 4), and several areas of caseation were present. One calcified area contained bone with a small area of bone marrow. The peripheral portions of the lungs were the site of unresolved and organizing pneumonia. Many large epithelial cells were noted in the alveoli, but these were diffusely distributed and did not suggest tumor

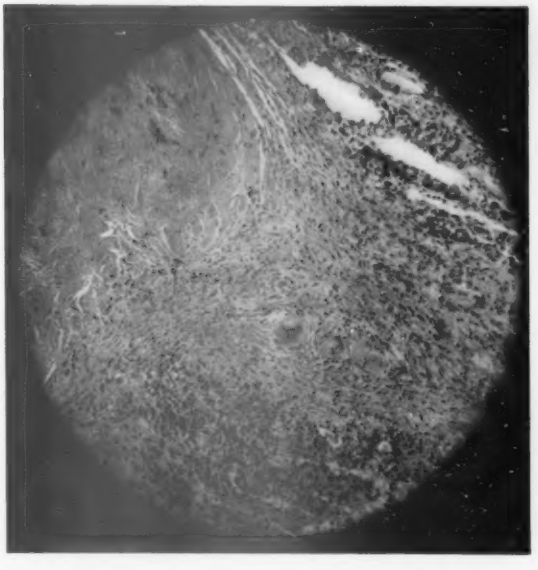

Fig. 4. Showing tubercle with giant cells in central portion and heavy fibrous tissue reaction.

growth. A few of the vessels contained organized and canalized thrombi.

Examination of the remaining organs revealed no lesions relevant to this report, except that a few early miliary tubercles were seen in the spleen.

Pathological Diagnosis: Silicosis and tuberculosis at the pulmonary hilum; pneumonia with delayed resolution and partial organization.

Chemical examination of the lung tissue by Dr. Frank L. Kozelka of the Department of Pharmacology and Toxicology gave the following results:

	Grams— dry wt.	Ash	SiO_2
Sample I	3.0355	2.18%	0.92%
Sample II	5.8873	2.23%	0.92%

Expressed differently, each sample contained 9.2 mg. of SiO_2 per gram of dried tissue, which is far above the 1.13 mg. determined by McNally[1] as the average content for normal lung.

COMMENT

In reviewing this case, even in the light of the post-mortem findings, we still believe that a roentgenological diagnosis of neoplasm was justifiable. The only question arising at the time of the radiological consultation was as to the specific nature of the process. Because it was bilateral one might have hesitated to look upon it as a primary bronchial malignancy, since the supposed metastatic extension occurred in a manner which is quite unusual with this disease. One might have been more inclined to consider it a metastatic glandular lesion or a malignant lymphoma. While part of the radiopacity was perhaps due to atelectasis, it does not seem justified to explain it entirely on that basis, since the involvement followed neither lobe.

We are dealing with an extremely unusual distribution for silicosis, which is typically seen in the peripheral portions of the lung. The extreme dyspnea in this case was undoubtedly caused by the contraction of the hilar scar tissue about the main bronchial trunks.

SUMMARY

A case of silicosis and tuberculosis in a white male, aged thirty-six, is reported, which roentgenologically had the appearance of a neoplasm. There was no history of exposure to dust containing silica. The post-mortem findings and the results of the chemical examination of the lungs are given.*

[1] McNally, W. D. Silicon dioxide content of lungs in health and disease. *J. Am. M. Ass.*, 1933, *101*, 584–587. The normal lung contains 1.13 mg. SiO_2 per gram of dried tissue (0.113 per cent).

* Since submitting this paper for publication the following pertinent articles have been published: Bradshaw, H. H., and Chodoff, R. J. Anthracosilicosis simulating pulmonary carcinoma. *Am. Rev. Tuberc.*, 1939, *39*, 817–824. Holman, E., and Pierson, P. Carcinoma of the lung simulating inflammatory disease. *J. Am. M. Ass.*, 1939, *113*, 108–111.

Vol. 43, No. 1

FLUOROGRAPHY

THE PHOTOGRAPHY OF THE FLUORESCENT IMAGE

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IN HIS first paper on the discovery of the x-rays, Roentgen demonstrated both the fluorescent and photographic effects of the rays. In the period of enthusiastic experimentation which immediately followed the announcement of the discovery much ingenuity was shown in the efforts to establish the best technical method of recording the roentgen image.

The screen image, simple and easy in its attainment, instantaneous in its appearance, graphic in its visibility, seemed for the moment to be the most desirable and it was only logical to attempt to obtain a permanent record of this image by ordinary photography. Thus, already in April, 1896, six months after the discovery, Bleyer constructed and used an apparatus for photographing the fluorescent image, which he called the photofluoroscope. Bleyer thought the method had an advantage over the direct film method in that visual observation could be combined with the production of a permanent record then obtainable by photographic exposures of a few minutes. Among other early efforts in this direction may be mentioned that of McIntyre who, by the use of a lead shield around the lens aperture, remedied the fogging of the plates in the camera arising from the direct radiation passing through the screen.

But when Porcher (1897) after considerable experimentation discarded the method as impractical and as having no advantage whatever over direct roentgenography, he apparently expressed the opinion of most workers, for the method was abandoned in favor of the direct roentgenography which developed with remarkable strides from its crude beginnings to its present state.

However, the allure of the moving picture stimulated workers to investigate the possibility of an indirect method of its accomplishment and in 1907 Köhler, who was engaged in direct roentgen cinematography, mentioned photography of the fluorescent image as a promising future possibility, and in 1909, in association with Biesalski, described a practical method of fluororoentgenography utilizing a screen of calcium tungstate (blue fluorescence), a camera with an F 2.0 lens and a mirror which permitted placing the camera outside of the beam of direct radiation. Biesalski also used a concave mirror instead of a lens by means of which he could obtain a much greater effective optical aperture.

It was apparent that the future development of the method depended on the possibility of obtaining lenses of greater aperture, screens of brilliant luminescence and photographic films of high sensitivity.

In a paper entitled, "Photography of the Fluorescent Screen for Roentgen Kinematography and other Purposes," read before the Philadelphia Roentgen Society on March 24, 1911, Caldwell presented all the basic and essential principles underlying the application of fluorography and foreshadowed its present-day application with prophetic instinct and scientific acumen. He used a 4×5 camera with a Cooke lens, working at aperture F 4.5 and a "Gehler folie" screen which had phosphorescent (after glow) as well as high actinic fluorescence. To determine whether the "after glow" would interfere with making successful photographs of the screen in rapid succession, he attached the screen to a rotating disc and exposed it to roentgen rays through a narrow radial slit in a sheet of lead. A brilliant narrow line of fluorescence was produced on the screen. It was necessary to rotate the screen at an exceedingly high rate of speed in order to materially widen the brilliantly fluorescing portion, indicating that "after glow" was of no practical importance as a contaminating

factor.* The photographs he obtained of the extremities, lungs and thorax were full of rich detail and, as he had hoped, the camera recorded much more than the eye could see on the fluorescent screen.

Caldwell pointed out the advantages of the method, the low cost, the simplification of the problems of filing and transportation. He prophesied that with the development of screens of higher actinic properties, photographic films of greater sensitivity, lenses of greater speed and more intense excitation by roentgen rays, the method would attain a great practical value and would revolutionize roentgenography.†

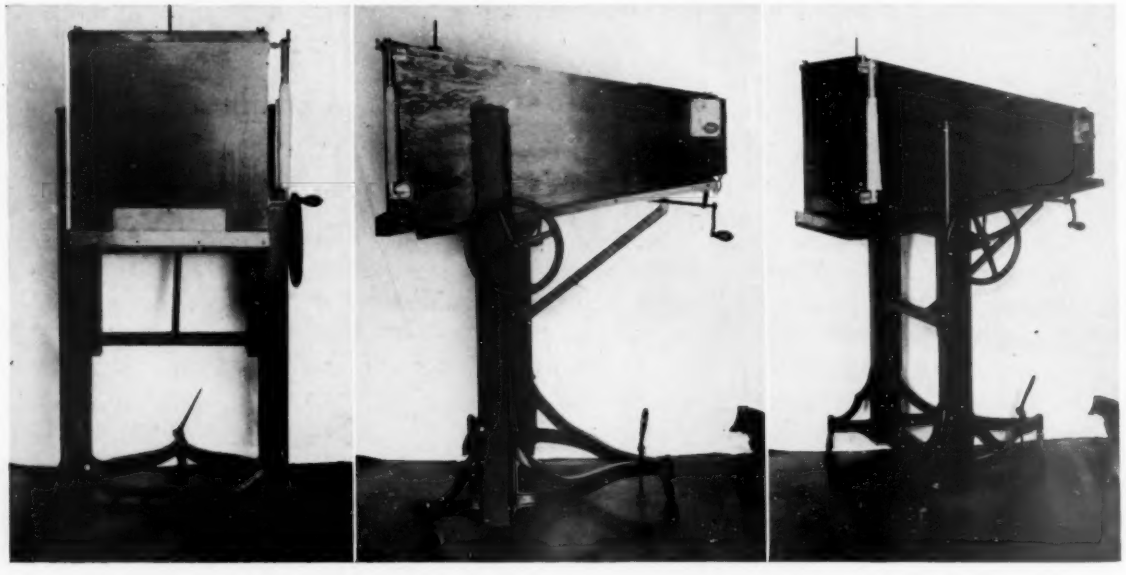

FIG. 1. Three views of fluorographic apparatus.

In 1913 Loman and Camandon used an F 1.55 lens with a specially sensitized film. Luboshez made use of an F .625 lens and still more recently Dariaux and Djian, a lens of aperture F .53. Others who should be mentioned in connection with this work are Reynolds, Reiser, and Schinzel, who in a patent suggested the use of a screen bent into a surface concave toward the lens so as to correct for some of the optical errors of the wide aperture lenses. The great improvement in recent years in fluorescent screens by Leonard Levy of London and in photographic materials, is responsible for the development of the method to such a state that its practical and routine application is now possible.

De Abreu's work (Brazil) in 1930 represents the first large scale application of the method. In fact modern fluorography owes its present status to his ingenuity and enthusiasm. Many technical improvements have been devised by Janker (1938).

My own interest in this work is due entirely to the inspiration of de Abreu, whose graphic demonstration of the application of this method convinced me of the practical applicability to diagnostic roentgenology.

APPARATUS AND TECHNIQUE

The apparatus consists essentially of a light-proof box of pyramidal shape with a fluoroscopic screen mounted on one end, a camera at the other, and means for ad-

* This experiment, made twenty-eight years ago, has a bearing on modern fluorography as the most sensitive fluorescent screen now available, the "fluorazure" screen also shows an "after glow," but not sufficient to interfere with the recording of a clear image.

† I have gone into detail regarding Caldwell's work because of the various claims which have been made for priority in this field.

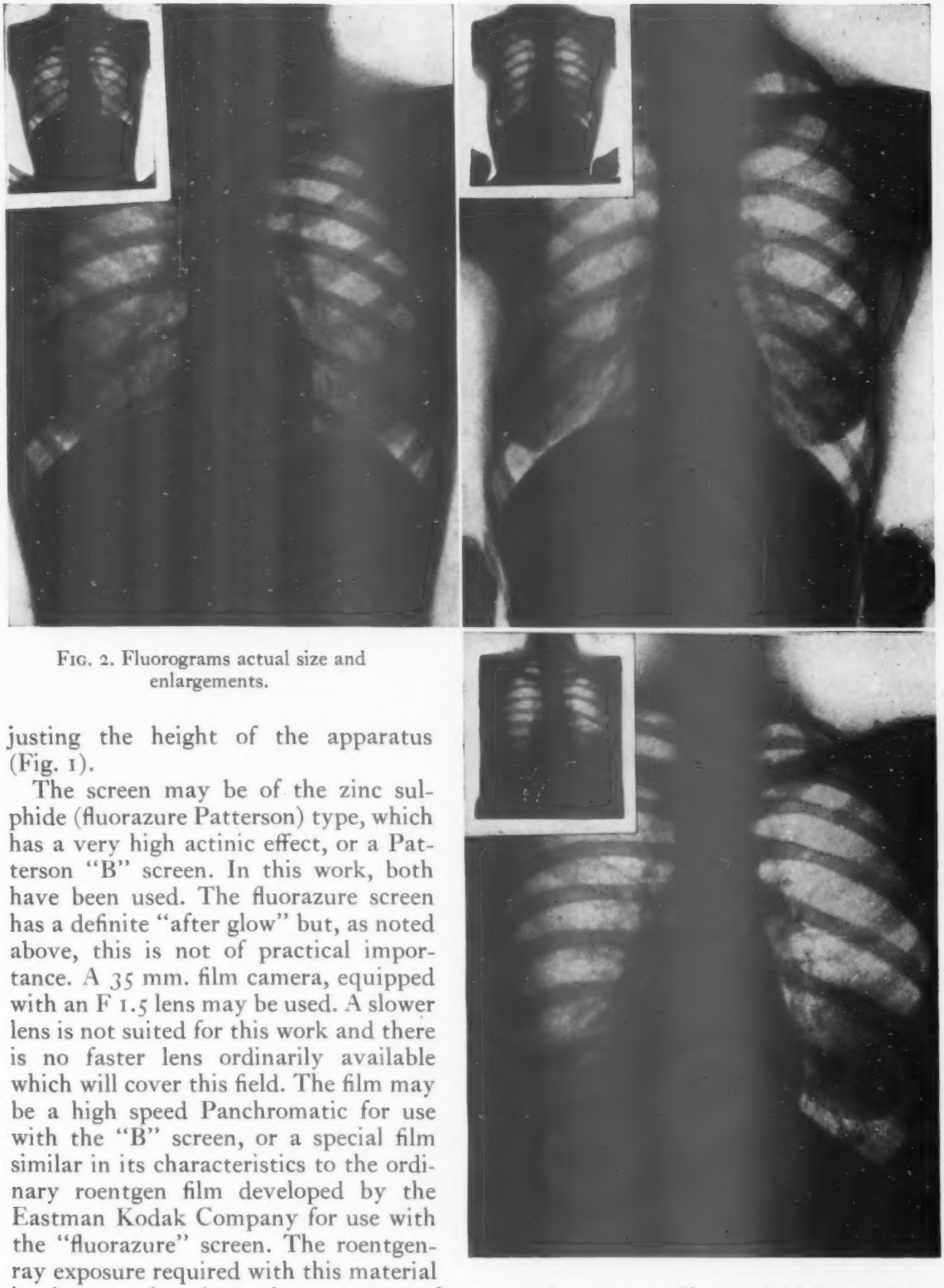

Fig. 2. Fluorograms actual size and enlargements.

justing the height of the apparatus (Fig. 1).

The screen may be of the zinc sulphide (fluorazure Patterson) type, which has a very high actinic effect, or a Patterson "B" screen. In this work, both have been used. The fluorazure screen has a definite "after glow" but, as noted above, this is not of practical importance. A 35 mm. film camera, equipped with an F 1.5 lens may be used. A slower lens is not suited for this work and there is no faster lens ordinarily available which will cover this field. The film may be a high speed Panchromatic for use with the "B" screen, or a special film similar in its characteristics to the ordinary roentgen film developed by the Eastman Kodak Company for use with the "fluorazure" screen. The roentgen-ray exposure required with this material is about twelve times that necessary for the same subject with the standard double-coated roentgen film and high-speed intensifying screens. For the average chest,

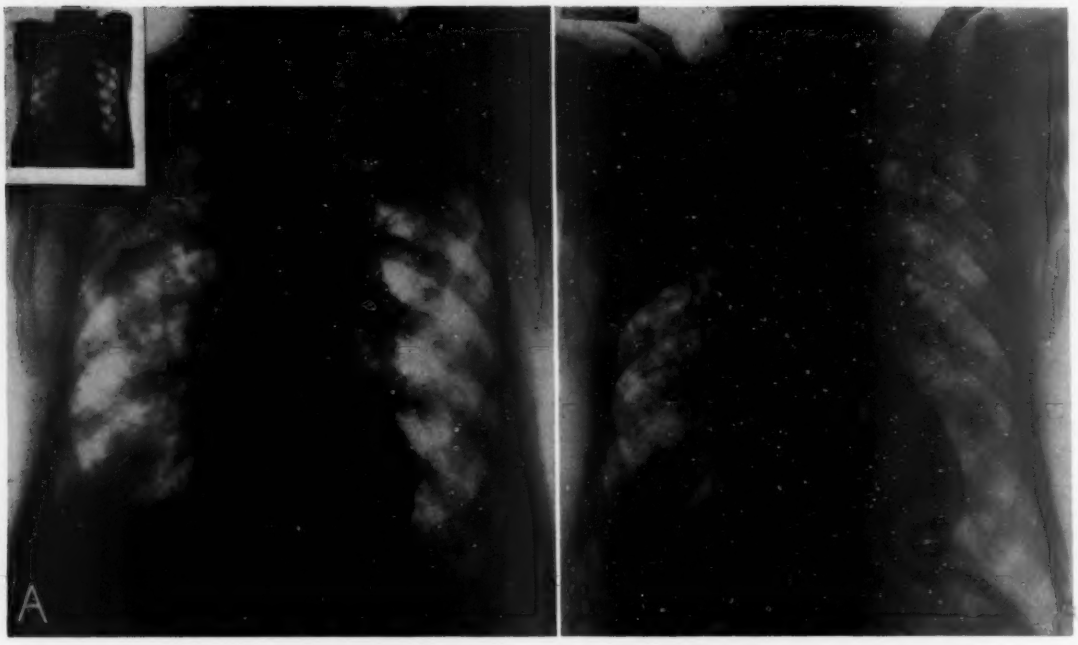

FIG. 3. Exudative and fibroid phthisis of both lungs. *A*, fluorogram and enlargement; *B*, reduction of regular teleroentgenogram.

80 kv. (peak), 150 ma. and 1/10 second exposure at 30 inch tube-screen distance is necessary.

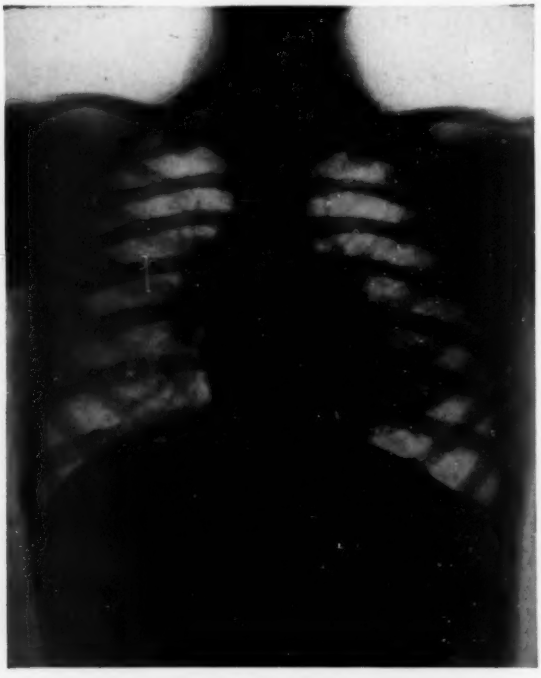

FIG. 4. Ghon focus, right lung—enlargement from fluorogram.

The camera is mounted at a distance of 90 cm. from the screen, the focus of the lens being determined once and for all by trial exposures. The camera is removable for the loading and unloading of 150 cm. of 35 mm. film, enough for thirty-six exposures. Mechanical means are provided for the winding of the film and operation of the shutter from the outside of the box. The number of exposures made is recorded on an automatic counter.

A positive method of film identification is necessary because the ordinary lead numbers are not always legible. To avoid this difficulty, the numbers and letters are recorded optically by a method similar to that used by Janker. Two light-proof slots are arranged below the screen for the insertion of white cards bearing identifying information written in black ink. Small lights inside the box illuminate these cards in such a manner that no stray light reaches the screen. These lights are controlled by a switch on the outside of the box, where a pilot light in series with the marking lights indicates that this recording feature operates properly.

The processing of the strips requires scrupulous attention to small details. Insignificant dirt particles and scratches may ruin an otherwise good film. All solutions should be filtered, and the film should be processed in a suitable tank, different types of which are on the market.

VIEWING OF THE FLUOROGRAMS

After development, the strip bears eight fluorograms per foot of film. These may be viewed: (1) By a magnifying lens. An arrangement may be made by which the film is drawn over an illuminated surface, above which is mounted a magnifying glass. (2) By projection. By projecting the film to a magnification of 6.8 times, an image is obtained which is 15 per cent smaller than half-size of the original screen image. For the average chest, this just compensates for the distortion due to the use of 30 inch target-screen distance. Thus the projected image, under these conditions, is a true half-size representation of the chest in the average case. A good projector and a grainless screen are necessary for optimum results. The screen and projector are conveniently mounted on a single board which may be used as a unit. The film may of course also be projected to the usual full size lecture hall screen.

FILING AND STORAGE

The entire roll of films may be filed in holes in a board, as is done by de Abreu, or, if cut into short strips, mounted in book form behind celluloid, as by Janker. But for hospital work, where the films must be repeatedly consulted, it appears preferable to mount each film individually in 2″×2″ slides, with a paper mask on which is written any information desired. Such a mount avoids the inevitable scratching which occurs if the film strips are handled frequently. These slides are filed in shallow filing cases.

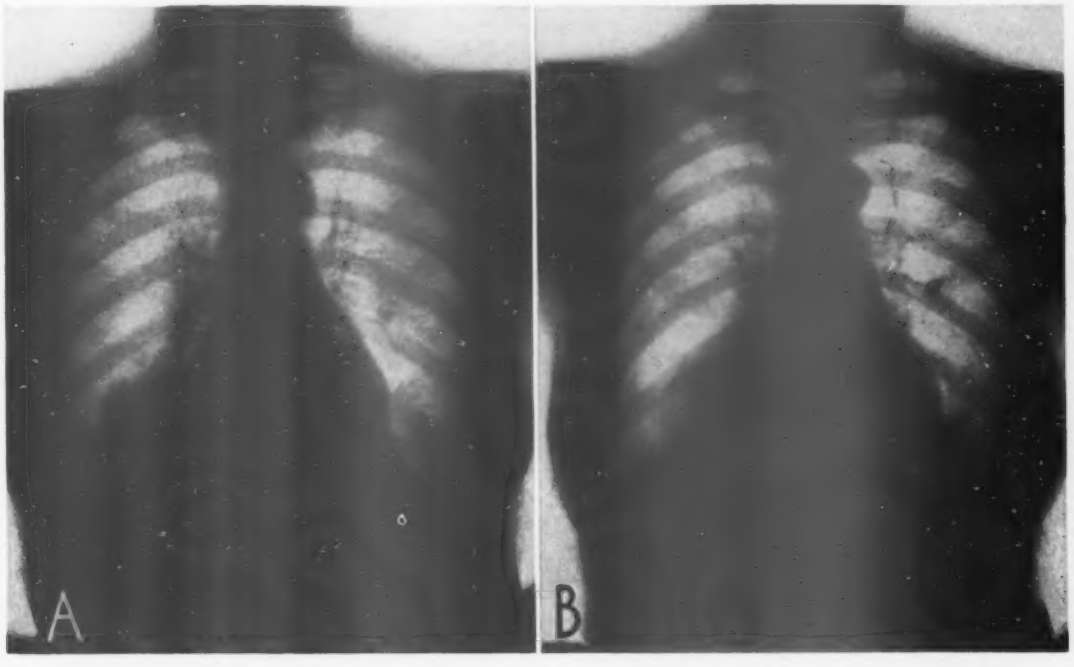

Fig. 5. *A*, tumor right lower lobe; tracheobronchial nodes; *B*, after pneumothorax—enlargements from fluorograms.

EVALUATION

This fluorographic method is just now not intended as a substitute for the usual

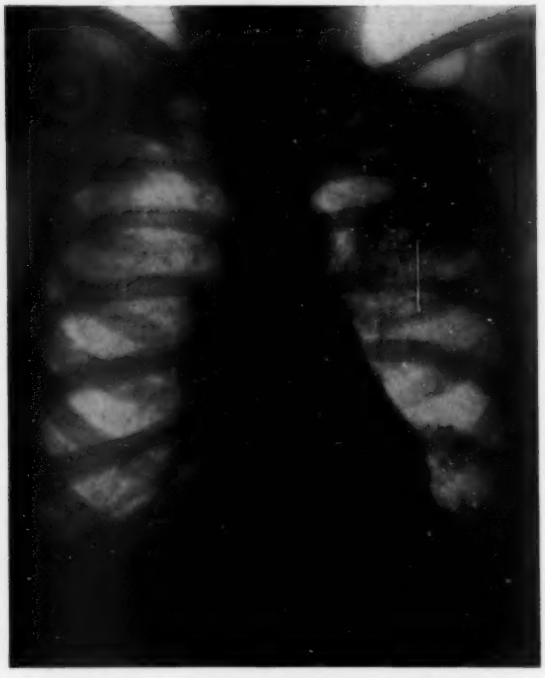

FIG. 6. Fibroid apical tuberculosis, left upper lobe extension—enlargement from fluorogram.

roentgenogram, though it seems to be developing in this direction. Generally speaking, it may be said that the record is superior to the fluoroscopic examination, not only because of the better visibility of detail, but also because it has the obvious advantage of furnishing a permanent record of the fluoroscopic image. It is well known that changes in the lung can be visualized fluoroscopically only if they have a certain size, and tests have shown that changes of small areas can be visualized on the fluorographic record which cannot be seen fluoroscopically. It is of course conceded that the small fluorographic film in no way compares with the regular film in the sharpness of the detail and contrast. But for a general gross survey of the chest, with the view of determining whether or not pathological conditions exist, the small fluorographic film may well serve as a substitute for fluoroscopy and for the regular film. For the study of the characteristics of the lesion, however, the large film is obviously the best record.

The paramount advantage of fluorography is the reduction in the cost of the examination, particularly in thoracic and gastrointestinal work. The usual film of the chest (14″×17″—238 square inches) costs about 50 cents, while the film used in fluorography measures 2 square inches and costs but 2 per cent of the large film. This low cost makes possible the examination of large groups and permits roentgen-ray surveys of whole populations—an application of tremendous social value. It makes possible the routine examination of the chest and gastrointestinal tracts, for instance, of all admissions to the hospitals, and will undoubtedly aid in the early diagnosis of many diseases of the lungs, heart, mediastinum and gastrointestinal tract.

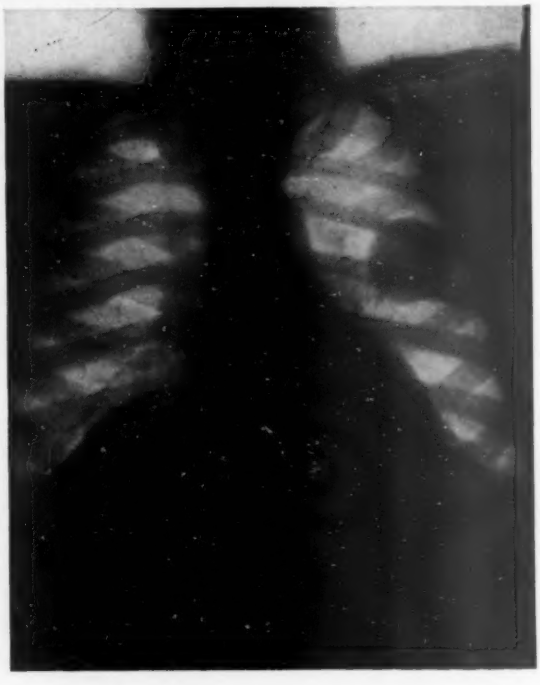

FIG. 7. Metastatic tumor left lung—enlargement from fluorogram.

APPLICABILITY

1. Fluorography is applicable to the study of the skeleton, delineating gross bone changes and deformities.*

* For some years I have been making large films, 20×36 inches, for the study of the relationship of habitus to visceral morphology, but the high cost of the roentgenograms has impeded this

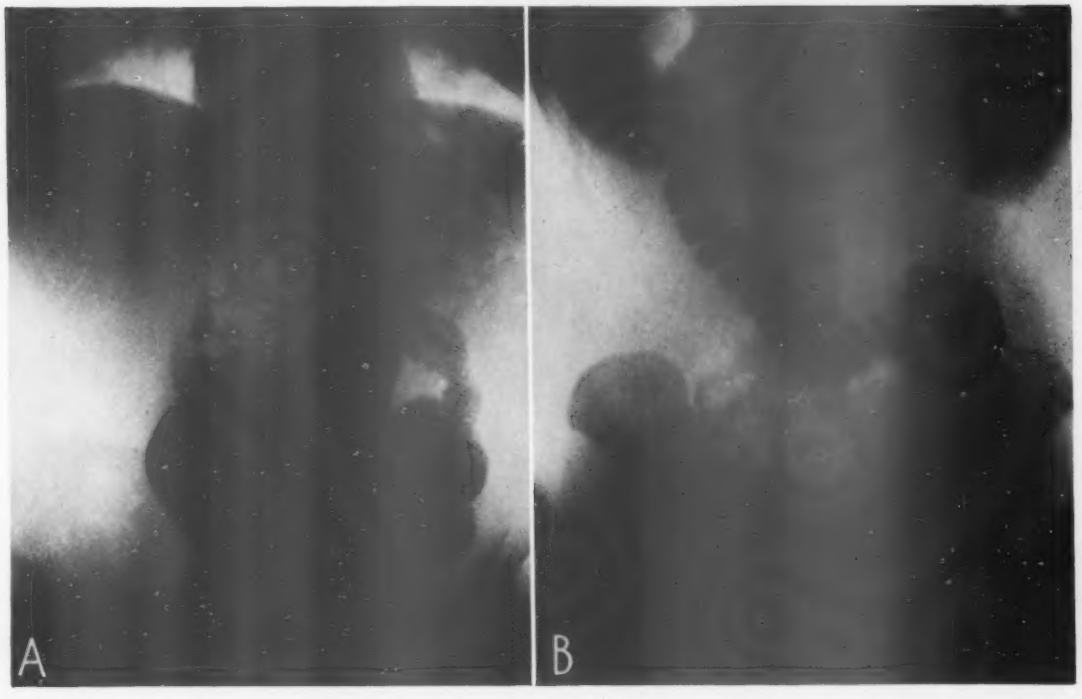

Fig. 8. *A*, normal stomach and small intestine; *B*, normal colon—enlargements from fluorograms.

2. It is useful in gastrointestinal surveys, particularly in the study of the colon, and in motility tests.

3. It gives clearly the position and shape of the heart and, if suitable correction factors are used, the heart shadow diameters may be determined according to the usual method.

4. Its greatest field of usefulness is in the study of the lungs, particularly for the determination of tuberculous changes. It is not intended as a method of fine differentiation as to the type of lesion, but the early apical infiltration, the cavity, the fibrotic and calcific changes are demonstrable. The image of the pulmonic fields has neither the contrast nor the detail of the large film but, nevertheless, the record is sufficiently clear to permit the differentiation of the normal from the abnormal lung.

I desire to acknowledge the invaluable assistance rendered by Myron Schwarzschild in the construction and testing of the apparatus.

work. By fluorography, however, it now becomes possible to make such examinations of large groups at a very low cost.

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Vol. 43, No. 1

OSTEOFIBROMA OF THE CRANIUM

FROM A ROENTGENOLOGIC VIEWPOINT*

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IN 1891, von Recklinghausen described the disease called osteitis fibrosa, and since then there have been many publications dealing with this interesting condition. Almost all articles and references dealing with osteitis fibrosa, or osteitis fibrosa cystica, discuss the bone changes in the skeleton below the neck, with but few exceptions which usually refer to the changes produced in the jaws. It is extremely rare to find references in the literature dealing with lesions involving the skull bones, and for that reason this discussion is offered.

The etiology of osteitis fibrosa is not well understood. When the condition is widespread and affects many bones of the skeleton, most of the evidence points to its being the result of an increase in parathyroid activity. When we find localized areas of osteitis fibrosa, such as solitary bone cysts or particularly lesions of the skull, it seems highly improbable that the parathyroids are at fault. The lesions, as we see them in the bones of the vault, are not predominantly cystic. In fact the presence of a cystic tendency may be difficult to recognize because the osteofibrosis often obliterates the cysts even if they are potentially present. The disease is nearly always found in young people.

It may be of interest to note that the cases forming the basis for this discussion were only 5 in number, but they had many points in common. The body chemistry was apparently normal as far as could be determined by the usual tests, which have always seemed to me to leave a lot to be desired. In all 5 cases one of the first objective symptoms to be noted was local tenderness and tumefaction. One case complained of "dizzy spells" and one-sided headaches. Two cases gave histories of trauma to the involved area, preceding by an indefinite time the onset of the symptoms. In one case there was a feeling of general malaise and dull generalized headaches.

When osteitis fibrosa occurs in the skull, the disease is most apt to attack the bones of membranous origin which include the vault. The lesions originate usually in the diploe, and produce osteolysis of the outer table before involving the inner table. Usually there is some tumefaction in which giant cells predominate, and it is this tumor formation that may bulge inward giving rise to symptoms of localized cerebral pressure. The disease is no respecter of suture lines, and may spread widely, which is not uncommon, or it may remain as a small localized lesion, but the tendency is toward gradual enlargement.

The case illustrated in Figure 2 was the first of the series, and there was considerable discussion as to what the diagnosis might be, so in order to be sure, a biopsy was done and the microscopic findings were reported as follows by Dr. Arthur Purdy Stout:

(1) The outer table shows an intertrabecular fibrosis in part of the bone while the rest of it shows normal bone and bone marrow.

(2) The specimen removed from beneath the outer table shows that the cancellous bone has had its trabeculae greatly widened by the growth of exceedingly dense and relatively avascular fibrous tissue. The bone trabeculae in this area appear inactive, showing no evidence of proliferation nor of erosion. This zone merges at one end with a more vascular, granulomatous tissue in which there are a large number of multinucleated phagocytic giant cells, some of which are vacuolated. In this tissue there is no bone or osteoid found. This

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FIG. 1. Osteofibroma. The lesion involves the superior portion of the left parietal bone. The bone is thickened and appears mottled, but there is no increased vascularity.

is the tissue which formed the lining of the hemorrhage-filled cavity.

(3) The wall of the hematoma consists of a granulomatous tissue with large numbers of multinucleated phagocytic giant cells. Adherent to the inner surface is some partly organized blood clot.

This lesion is similar to that found in the majority of cases of osteitis fibrosa. The intertrabecular fibrosis extends outward from the cystic area somewhat further than in the usual case, although not very much further. This cannot be regarded as sufficient to invalidate the diagnosis. It is quite usual to find the periphery of the lesion almost exclusively fibrous while the portion of it which comes into contact with the blood clot is vascular, granulomatous, and contains large numbers of multinucleated giant phagocytes. In none of the sections is there any evidence of bone proliferation.

Diagnosis: Osteitis fibrosa cystica of frontal and parietal bones.

In discussing with Dr. Stout the characteristics of this particular form of osteitis fibrosa cystica, which might be termed osteitis fibrosa localisata, the question arose as to whether or not there was any difference between this local manifestation and the generalized form of the disease caused by parathyroidal overactivity. He was strongly of the opinion that microscopically the conditions were identical, but agreed that the localized form as seen in the calvarium might be termed an osteofibroma so as not to confuse the two clinically and roentgenologically.

Hyperparathyroidism, when caused by a tumor of the parathyroids, produces bone changes which Dr. Stout feels cannot be differentiated microscopically, as a rule, from the changes of osteitis fibrosa cystica. This, in spite of the fact that hyperparathyroidism when seen in the skull is quite different roentgenologically (see Fig. 7). It is also of interest to note that if the parathyroid tumor is completely removed, the bones of the skull rapidly tend to revert to a comparatively normal appearance which seems to indicate that the bone structure is not permanently disoriented, although the bone in the presence of an osteofibroma is permanently changed. Evidently the bone reaction up to a certain point is quite similar in the two conditions, but tends to be more profound in the case of osteitis fibrosa.

FIG. 2. Osteofibroma. The lesion is widespread through the frontal and anterior parietal regions. The defect in the extreme frontal region is the result of a biopsy.

In making a differential diagnosis of an osteofibroma, one must first exclude the possibility of the bone changes being caused by a meningiotheliomatous or "en plaque" type of meningioma. This may be difficult at times but usually it is possible to see in good stereoscopic films that there is no spiculation which is likely to be present with a meningioma, and also there will be no alteration in the vascularity. As a rule, the symptoms would be much less marked with an osteofibroma than they would be in the presence of a meningioma; and in its early stages, the meningioma would involve the inner table before the outer table would show any changes.

Fig. 3. Osteofibroma. The lesion is frontal and has produced some fusiform swelling of the outer table.

Metastatic malignant tumors at times may simulate the roentgenographic bone changes of an osteofibroma. Lesions caused by metastatic tumors are almost always multiple and chiefly osteolytic. The bone structure is actually destroyed and there is little or no attempt at repair, which is not usual with an osteofibroma. The history of the case would help to rule out metastatic disease.

Osteomyelitis, particularly the luetic variety, might produce a lesion almost identical with an osteofibroma. In fact, the history and clinical findings might be necessary to differentiate between these two conditions. The lesions of osteomyelitis are not apt to produce any tumefaction except the luetic type which often is accompanied by an overlying gumma. Osteomyelitic changes are prone to stop at suture lines but at times they will follow along the suture lines particularly in children. Osteolysis is often predominant, and frequently about the edges there will be evidence of bone repair, particularly if the

Fig. 4. Osteofibroma. A small lesion appears in the occipitoparietal region.

Fig. 5. Osteofibroma. A frontoparietal lesion appears which is more predominantly osteolytic than is usually seen. Note the involvement of the outer table.

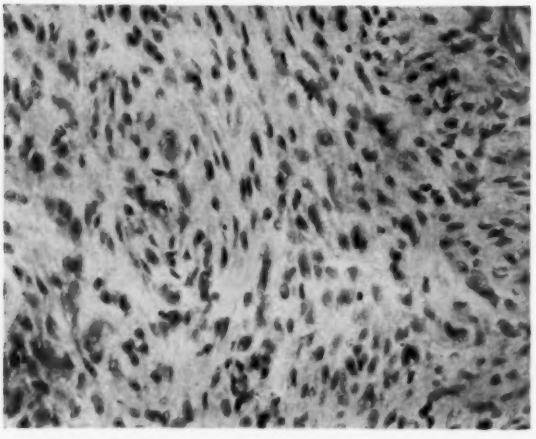

Fig. 6. Photomicrograph (×700) of biopsy section taken from case illustrated in Figure 2.

infection is old. Here again, the history will play an important rôle in the final differentiation.

A cavernous hemangioma of bone can produce a localized skull lesion. Such a lesion almost always gives rise to bony spiculation which will be of a radiating somewhat perpendicular type interspersed with myriads of small areas of decreased density not unlike numerous little insect eyes peering out from indentations in the bone. Such a change would not be caused by an osteofibroma.

A localized early Paget's disease could roughly simulate an osteofibroma. In fact the two diseases have many factors in common. Paget's disease is apt to be more widely spread and not so clearly localized. In the early stages these two conditions might be indistinguishable, provided the Paget's disease was markedly localized. Later on in the course of Paget's disease, the thickening of the calvarium and the tendency toward irregular osteoporosis would easily differentiate the lesion from that produced by an osteofibroma.

In brief, the roentgenographic appearance of an osteofibroma in the skull is characterized by an almost complete disorientation of bone structure, with no hypervascularity, no evidence of bone repair, some osteolysis, thickening of a fusiform type mostly through the outer table, and no spiculation. The history is usually unimpressive, and consists essentially of local tenderness with some indefinite form of mild headache.

The treatment of an osteofibroma is chiefly surgical. Radiation in fairly large, well filtered doses may be tried. The lesion progresses very slowly, so that no harm would be expected to follow a sufficient delay to give radiation a trial. Usually, however, radiotherapy will prove disappointing.

Fig. 7. Hyperparathyroidism. The granular appearance of the bones is almost characteristic of this disease. It is interesting to note that in this case the blood vessels of the meninges are calcified (arrows).

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THE EFFECT OF PEPTIC ULCER IN CHOLECYSTOGRAPHY

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IT IS believed by many authorities that peptic ulcer, because of the high acidity associated with it, is an important factor in many cases of non-filling of the gallbladder in cholecystography. Brailsford,[1] Robins and Goldberg,[2] Leb,[3] and others, emphasized the fact that non-filling of the gallbladder often occurs in cases of duodenal ulceration. Friedenwald, Feldman and Kearney,[4] in their investigation of the effect of gastric acidity on gallbladder visualization, found that the gallbladder shadows are often not as dense as those obtained in cases which have a normal acidity. In a series of cases of duodenal ulcer, with high gastric acidities, in which oral cholecystographic examinations were made, we[4] did not observe a single instance in which failure to visualize the gallbladder could be definitely attributed to high gastric acidity. These results were undoubtedly due to the large dosage of dye which had been administered. Boyden and Berman[5] observed a normal visualization of the gallbladder in 30 out of 33 cases (90.9 per cent) of peptic ulcer. We had believed that non-filling of the gallbladder, due to peptic ulceration, occasionally occurs, but is an uncommon observation.

Since there are many controversial opinions regarding the effect of peptic ulcer on cholecystography, a series of 115 consecutive cases of peptic ulcer was studied to determine the effect of peptic ulcer on the visualization of the gallbladder.

It is a definitely known fact that exceedingly high acidities of the stomach, with lowering of the pH of the intestinal content, plays a distinct rôle in changing the soluble tetraiodophenolphthalein dye into its insoluble compound. In cases of peptic ulcer, the density of the vesicle shadow is often reduced to a marked degree. It has been our experience that when a small dosage of tetraiodophenolphthalein was administered, non-filling of the gallbladder occasionally occurred. This could be overcome in many instances if an additional dose of dye were given immediately. When the larger dosage of the dye was administered in peptic ulcer cases, cholecystography ordinarily yielded a normal gallbladder shadow in the majority of cases.

In our series of 115 cases of peptic ulcer, 112 were duodenal and 3 gastric. These cases were carefully analyzed following cholecystography to study the effect of peptic ulceration and its associated high gastric acidity upon visualization of the gallbladder. Of the 115 cases, a satisfactory gallbladder shadow of normal density was obtained in 101, or 87.7 per cent. In 9, there were poor filling or faint shadows, and in 5, non-filling of the gallbladder. It is interesting to note that in the 3 cases of gastric ulceration, 2 filled well, and in the other there was a non-filling gallbladder. Gallstones were found in 6 instances, 4 of which revealed a normal filling and in 2 a poor filling gallbladder.

A study of the emptying of the gallbladder following a fat meal, consisting of two eggs and a glass of milk, was made to determine the effect of peptic ulcer on the contraction of the vesicle. Examinations were made from thirty to sixty minutes after the fat meal. Bronner[6] and Boyden and Berman,[5] point out that the rate of evacuation of the gallbladder is considerably accelerated in cases of peptic ulcer. In our study of gallbladder emptying, the size of the original filled vesicle shadow was taken as a standard, and the contraction was considered normal in those cases which contracted to less than half the original size; poor or sluggish contraction, in

those which were only slightly reduced in size, and non-contraction, in those which did not contract at all. In 110 visualized gallbladders, 80, or 72.7 per cent, responded normally following the fat meal. In 21 instances, or 19 per cent, there was a sluggish contraction, and in 9, or 8 per cent, no change in the size of the vesicle could be observed. In the 9 cases that failed to respond to the fat meal, 4 in the original films presented a faint shadow.

These studies were made from clinical and roentgenological observations in routine investigations of 115 consecutive cases of peptic ulcer. There were few surgical and no autopsy studies to confirm our findings. In the 9 cases which showed a poor filling or faint shadow of the gallbladder, only 2 were pathologically accounted for by the presence of gallstones: the remaining 7 cases and the 5 cases of non-filling gallbladders represent 10.4 per cent of the series which revealed abnormal cholecystographic findings. This percentage of abnormal cholecystograms seems rather high. In these cases there is some question of doubt whether or not the abnormal findings represent a pathological gallbladder or changes due to peptic ulceration. However, we are inclined to believe that some of these cases may be due to a pathological condition of the biliary tract, but many are probably due to peptic ulcer and the coexisting high gastric acidity. In those instances in which an abnormal cholecystographic finding occurs, the test can be repeated by utilizing the intravenous route to further support the observations made by the oral method. Even by the former procedure, the gallbladder may yield an abnormal cholecystographic test, as pointed out by Leb.[3] He performed intravenous cholecystography in 100 patients with duodenal ulcer and found that 26 per cent of organically healthy gallbladders failed to fill. These roentgen findings were confirmed in 25 cases which came to operation. The exact mechanism which produces a non-filling gallbladder by the intravenous method in cases of peptic ulceration has not been definitely explained. It is likely that dyskinesia of the gallbladder plays an important factor in these cases.

It is noteworthy to point out that dyskinetic changes of the gallbladder are commonly observed in the cholecystographic test in cases of peptic ulcer. In our series of 110 cases of filled gallbladders, 27.3 per cent revealed a sluggish or non-contracting gallbladder following a fat meal. Leb likewise directed attention to the fact that in many cases which showed signs of dyskinesia, the fat meal led to an accelerated or retarded evacuation of the gallbladder. He attributed this behavior of the gallbladder in cases of duodenal ulcer to the result of nervous irritative processes. Bronner and Boyden and Berman found an accelerated evacuation of the vesicle in peptic ulcer.

SUMMARY

Cholecystographic studies made in 115 cases of peptic ulcer revealed that the administration of a large dosage of dye usually tends to produce a more constant vesicle shadow of normal density than a smaller dosage. The larger dosage also probably reduces the number of cases of abnormal cholecystograms in peptic ulcer. Although we had believed that peptic ulcer had little practical significance on the filling or non-filling of the normal gallbladder, our observations reveal a rather high percentage (10.4 per cent) of abnormal filling in cases of peptic ulcer. In peptic ulcer there is frequently observed a dyskinesia of the gallbladder, resulting in its acceleration or retardation of emptying. In our series of cases of peptic ulcer, 27.3 per cent yielded a sluggish or non-contracting gallbladder. Of 115 cases of peptic ulcer, 6, or 5.2 per cent, were associated with gallstones. This study corroborates the general roentgenologic belief that peptic ulcer is undoubtedly responsible for many cases of non-filling of the gallbladder.

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GASTRIC NEURINOMA

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HISTORICAL INTRODUCTION

IT HAS only been within the last decade that attention has been directed to the occurrence of visceral neurinomas. Previously these tumors had only been described in the region of the central nervous system and peripheral nerves and had been designated as neurofibromas and peripheral gliomas. Since the time of Verocay's[18] work on the histology of these tumors they have been segregated as a distinct pathological entity and within the past decade the number of reported cases in the literature have become increasingly more frequent. Undoubtedly many cases of gastrointestinal neurinomas had previously been erroneously classed among the ganglioneuromas, neurofibromas, and sarcomas.

The very complex subject of tumors of nervous origin is made even more confusing by the large and varying nomenclature. We are dealing with a group of tumors which histologically have much in common and in spite of the varying terminology are closely interrelated. The French school under Masson[12] prefer the term gastric gliomas or schwannomas believing that they are ectodermal in origin and arise from the cells of the sheath of Schwann, while in the English literature there is shown a preference for the term perineurial fibroma or fibroblastoma.

INCIDENCE

Among all the benign tumors of the stomach the neurinoma is without doubt the rarest, although the neuromuscular apparatus of the stomach wall, especially in the lesser curvature, is abundant in nervous tissue. In a study of 2,168 neoplasms of the stomach by Eusterman and Senty,[9] only 27, or 1.3 per cent, were benign among which there was not one case of neurinoma. Minnes and Geschickter,[14] in a review of 50 cases of benign tumors of the stomach collected at Johns Hopkins, make no mention of gastric neurinoma. Balfour and Henderson[3] of the Mayo Clinic published 58 cases of benign tumors of the stomach without one neurinoma.

ETIOLOGY

These tumors are all thought to arise from the specialized investment which separates and insulates nervous tissue from the surrounding structures. In the stomach wall are to be found the same nerve plexuses which are present in the wall of the intestine, namely, the submucous plexus of Meissner and the myenteric plexus of Auerbach. The question of the etiology of gastric neurinomas will not be considered in detail as this represents a highly controversial subject. Masson[12] is a strong advocate of the neuro-ectodermal origin from the schwannian syncytium as opposed to the idea that these tumors are to be regarded as fibroblastomas arising from the perineurium or connective sheath of nerves, therefore a perineurial fibroblastoma.

Enormous proliferative changes in the nerves of the stomach wall in the neighborhood of inflamed gastric mucosa and gastric ulcers have been described which are thought to be the result of progressive inflammatory antecedents. These have been studied by Masson[13] in the walls of obliterated appendices and by Askanazy[1] in the wall of the stomach adjacent to gastric ulcers. The latter found in the cicatricial areas of gastric ulcers a pathological abundance of nerve fasciculi. This may reach considerable proportions, as in the case cited by Dupuy,[8] in which pathological examination of the stomach of a case of attempted suicide by means of hydrochloric acid ingestion showed a diffuse intramuscu-

lar neuroma, resulting in the formation of plexiform nerve fibers and ganglia accompanying an inflammatory lesion of the mucosa and submucosa. The relationship between these nervous proliferations and true benign gastric new growths of nervous origin is highly speculative.

PATHOLOGY

The benign tumors of the stomach with nervous elements have been divided into three categories: (1) ganglioneuromas, (2) neurofibromas, and (3) neurinomas or schwannomas. It is with the last group that we are here primarily concerned.

These tumors are grossly soft, elastic, well circumscribed, spherical, often lobulated and pedunculated, although they may be attached to the stomach wall by a broad base. They are said to occur most frequently on the posterior wall of the stomach, frequently near the lesser curvature. They are usually single, covered by mucous membrane which is very vascular and may be thickened, and may or may not be ulcerated. Frequently, because of their size and location, they interfere with the circulation to the overlying mucosa resulting in necrosis and ulceration. The presence of ulceration accounts for the very characteristic "en face" niche so frequently seen on the roentgenogram.

Microscopically the picture is very characteristic in the palisade arrangement of the elongated nuclei. According to Masson[12] "the specific cells of this tumor are connected in a syncytium like Schwann cells; they possess elongated nuclei and they are grouped in networks, in bundles and in palisades. These latter structures are pathognomonic. The palisades consist of oval nuclei aligned in the same transverse plane 'like staves on a barrel' (Verocay). On each side of this nuclear palisade, or on one side only, there is a fibrillar band parallel to it. The fibrils are oriented like the nuclei, running perpendicular to the nuclear band. Thus a palisade system is formed by two nuclear palisades parallel to each other and an intervening fibrillar palisade."

These tumors are mostly benign although Carnot's[6] case showed cell proliferation of a sarcomatous character. Denecke reports 2 cases of metastasizing neurinoma of the gastrointestinal tract, one occurring in the duodenum as a pedunculated tumor, the other a lobulated endogastric tumor arising from the greater curvature of the stomach. Both cases at autopsy showed extensive liver metastases.

CLINICAL MANIFESTATIONS

There are no characteristic clinical signs associated with gastric neurinomas which would not be manifested by any gastric lesion either inflammatory or new growth. Hemorrhage occurs in a surprisingly large number of the cases where ulceration of the tumor is present. Hortolomei and Burghele[10] report a case with massive severe hematemesis without previous gastric manifestations in the history. The frequent occurrence on the posterior wall of the stomach may favor hemorrhage either in the form of melena or hematemesis.

Rarely is a mass to be palpated, as in the case reported by Barber,[4] in which the patient noted a large, freely movable, painless mass in the upper quadrant of the abdomen, which showed no change in size and remained symptomless for nine years. Iceton, Poate and Tebbutt[11] report a case with pain across the upper abdomen, vomiting, and constipation. Death resulted from collapse following repeated severe melena. At autopsy the tumor which was attached to the greater curvature of the stomach had prolapsed through the pylorus producing gastric intussusception. In Ritter's[16] case the rhythmically recurring boring pain in the epigastrium, regularly related to meals, unaffected by diet and producing severe night pain, strongly simulated those of an ulcer, with a suggestion of possible perforation.

ROENTGEN DIAGNOSIS

The diagnosis is best made preopera-

tively by means of the roentgen examination from which, in typical cases, the exact diagnosis can be strongly suspected. Characteristically it presents an oval to round smoothly outlined defect with an "en face" niche. The defect is usually on the gastric walls leaving the curvatures free and regular. The smooth, well circumscribed appearance situated away from the gastric curvatures lends weight to the diagnosis of a benign tumor. Retention is not present unless the tumor is close enough to the pylorus to produce obstruction by prolapse. Peristalsis is undisturbed and a study of the mucous membrane pattern in the region of the tumor shows neither the radiation of the rugal folds suggestive of an ulcer nor the sudden termination as in malignancy. The presence of several irregular flecks of contrast material would indicate the existence of several ulcerations and would suggest the roentgen image of a degenerating malignancy.

REPORT OF CASE

A. P. (No. 94134), female, white, married, aged sixty, admitted May 10, 1938, with the chief complaint of having vomited blood the morning of admission and the night previous. The patient has had no previous admissions. The onset of the present illness began approximately four and one-half years ago at which time the patient began to have occasional pains in the epigastrium usually several hours after meals and relieved by alkalis. These episodes would occur two or three times weekly though with no great regularity and were occasionally accompanied by nausea and vomiting. In June, 1934, the patient had an attack of hematemesis following an exacerbation of her gastric distress and states that she vomited about a pint of dark blood. She remained in bed at that time for about three weeks and was placed on a soft diet by her physician. After her recovery the patient discontinued her diet and had a recurrence of hematemesis three years ago, following which she remained in bed for about a week. For the past three years there has been no repetition of the hematemesis although the gastric pains have persisted with the same regularity and with no increase in severity. The pains may occur two or three times weekly and then may be absent for two or three weeks.

One week before admission the patient began to have the gastric pains several times a day accompanied by nausea. The pain occurs usually about two hours after meals, starts in the epigastrium, has apparently not been severe, and seems to radiate downward. The evening before admission the patient had a fairly severe pain in her epigastrium and felt nauseated. A short time later she vomited about one pint of coffee ground vomitus and felt dizzy and weak. On the morning of admission the patient had several tarry stools and was seized with a moderately severe pain in the epigastrium and became nauseated and vomited about one pint of bright red blood.

The physical examination revealed some tenderness in the epigastrium and around the umbilicus. A few cardiac extrasystoles were noted. The immediate treatment consisted of blood transfusions, intravenous glucose, and the Meulengracht diet, to which the patient readily responded. A gastroscopic examination was done which revealed a deep ulcerative lesion at about the angulus on the lesser curvature of the stomach. The lesion appeared sharply defined and its upper border was about 9 cm. from the cardiac end. No evidence of gastritis elsewhere in the stomach. The gastroscopic impression was malignant ulcer (Schindler Type 2), operable.

Gastrointestinal series showed an "en face" ulcer niche measuring about 2 cm. in diameter on the posterior wall of the stomach near the lesser curvature in the middle third of the stomach (Fig. 1). There was some tenderness over the ulcer but no mass could be palpated through the abdominal wall in this region. The blood Kahn reaction was negative. Blood urea determinations showed progressive fall from 29 mg. per 100 cc. on May 10 to 15 mg. per 100 cc. on May 13.

The patient was operated on May 26 and a sleeve resection of the ulcer with wide margins was done with end-to-end anastomosis. Exploration at the time of operation revealed a hard crater-like ulcer at the junction of the upper and middle thirds of the stomach near the lesser curvature. The ulcer and surrounding reaction was about $1\frac{1}{2}$ inches in diameter and the crater was about $\frac{3}{4}$ inch deep. Complete inspection of the regional glands showed no evidence of metastasis.

FIG. 1. Roentgenogram made in the exaggerated left anterior oblique position showing large "en face" niche, indicated by arrow.

Pathological Report. Dr. Ralph H. Fuller. Buried in the wall of the stomach, overlying a line of omental attachment, is an encapsulated, spheroid, solid tissue mass measuring 3 cm. in diameter (Fig. 2). The substance of the tumor is firm, gray and homogeneous. The cut surface does not present the characteristically whorled appearance of interlacing bundles of fibers cut in various planes so commonly seen in myomas and fibromas. There is no apparent displacement of serosa or serosal supporting tissue by the mass which bulges into the lumen of the stomach producing a smoothly rounded hillock having a broad circular base. The gastric mucosa, only loosely attached to the capsule of the tumor mass, is everywhere of normal thinness and intact save at the apex of the hillock. Here there is an ulcer measuring 1 by 2 cm., without evidence of epithelial overgrowth at the ulcer margins. The ulcer crater perforates the capsule of the tumor and penetrates to a depth of 2 cm. in the tumor mass.

FIG. 2. Specimen of stomach wall removed at operation showing spheroid, solid tissue mass, bulging into the lumen of the stomach with central ulceration.

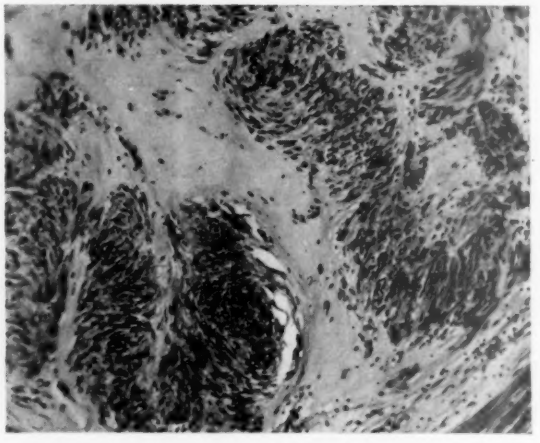

FIG. 3. Low magnification showing hyaline ground substance and bands of cellularity with whorls, eddies and palisading nuclei. Hematoxylin-eosin stain.

Microscopically the tumor is composed of hyaline or loose reticular substance supporting ribbon-like ranks of palisaded elongated nuclei. The ranks of nuclei appear irregularly to branch and anastomose presenting numerous whorls and eddies (Fig. 3). In the hyaline sup-

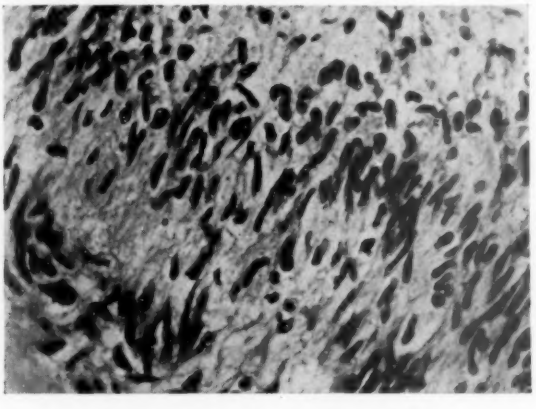

FIG. 4. High magnification of a cellular field. Hematoxylin-eosin stain.

porting substance there are scattered small areas in which calcium salts have been precipitated. The relatively avascular tumor mass is perfectly encapsulated. There is a narrow superficial zone of necrosis and acute inflammatory reaction in the floor of the ulcer.

Diagnosis. Benign neurinoma (perineurial fibroma or schwannoma) of the stomach.

SUMMARY

(1) Increasing familiarity with and more accurate interpretation of the histologic findings in gastric neurinomas has resulted in a marked increase in the number of cases reported in the literature of the past decade.

(2) The characteristic histological findings of elongated nuclei with a palisade formation, "like the staves of a barrel" grouped in networks, and bundles and presenting numerous whorls and eddies is emphasized.

(3) Hemorrhage, either in the form of melena or hematemesis, is a common clinical finding in gastric neurinomas.

(4) The roentgen findings may be sufficiently characteristic to permit of an accurate preoperative diagnosis. Classically this is an oval to round, smoothly outlined defect with an "en face" niche, usually located on the posterior wall of the stomach, leaving the curvatures regular and undisturbed.

(5) Most cases of gastric neurinomas are benign although malignant transformation has been recorded.

I wish to make grateful acknowledgment of the kindness extended me by Drs. Mont R. Reid and Leon Schiff of the staff of the Cincinnati General Hospital for making the clinical record of this case available to me, and to Dr. H. G. Reineke for his guidance and advice in the preparation of the manuscript.

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CONGENITAL SYNOSTOSIS OF THE CERVICO-THORACIC VERTEBRAE (THE KLIPPEL-FEIL SYNDROME)*

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HUTCHINSON[24] in 1894 described an anatomical specimen in which there was fusion of the vertebral bodies and a cleft of the arches from the third to the sixth cervical vertebra. The first clinical reference to this condition was the presentation by Clarke[7] in 1906.

The first comprehensive report in the literature of congenital synostosis of the cervical spine appeared in 1912 by Klippel and Feil.[28,29] This was the case of a male, aged forty-six, who died of pneumonia, and at necropsy showed complete fusion of the cervical spine and posterior spina bifida occulta. This condition has since been commonly designated as the "Klippel-Feil syndrome." It is referred to by the French as "l'homme sans cou" and by the Germans as "Kurzhals."

In 1919 Feil collected the records of 14 cases and by 1925 he and his collaborators[9–16] contributed 14 articles on the subject. A review of the literature shows a predominance of European reports. There are at least eighty-three articles reporting 133 cases. The noteworthy contributions are by Kallius,[26] and by Bertolotti,[4] who reported 18 cases and 9 cases respectively. Fourteen articles have appeared in the English and American literature reporting 28 cases. Meisinbach's[31] report in 1912 was the first to appear in the American literature. Since then the following have contributed articles on the subject: Noble and Frawley,[35] Greig,[21] and Willard and Nicholson.[44] Each reported 2 cases. Bauman[3] and Mitchell[33] have each reported 6 cases. The remaining presentations are individual case reports.[18,36,37,38,41,43]

American and English anatomists[6,19,20,32,34,42] in six articles reported 30 specimens of anomalous and congenitally deformed cervical spines. One such article[8] appeared in the French literature. This would seem to suggest that much of the clinical material observed has not been reported and that the condition, though infrequent, is probably not rare.

EMBRYOLOGIC CONSIDERATION[27]

The notochord, the most primitive form of axial support, appears in the human embryo from the third to the fifth week. Three stages are noted in the evolution of the spinal column: (1) Primitive segmentation (somites), (2) the cartilaginous stage in which the cells of the mesenchyme become modified into cartilage forming cells and (3) the final stage where cartilage is replaced by bone. These changes occur in rapid succession in the human embryo during the second month of gestation.

The neural tube is formed (third week) from a strip of ectoderm or epiblast from along the median dorsal line and ventral to it, the notochord in like manner from the archenteron. The paraxial mesoderm on either side becomes segmented. These segments, known as somites or protovertebrae, are separated from each other by septa. The notochord begins to disappear in the second month due to the action of the bodies of the vertebrae and parachordal cartilage which form about and constrict it. It only persists as the nucleus pulposus in the disc between the vertebral bodies.

In the membranous stage (fifth and sixth weeks) the vertebrae consist of a centrum surrounding the notochord and a horseshoe-shaped vertebral bow, the latter consisting of a right and left limb which become corresponding parts of the neural vertebral arch. These are united anterior to the centrum by the hypochordal bow. During the cartilaginous stage (sixth week), the entire fibrous base is transformed

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into cartilage and three centers of chondrification appear, one each for the neural arch, the costal process and the centrum. The vertebral bodies are formed opposite each intersegmental septum, and hence, each centrum is the product of two somites. At the fourth month the lateral cartilaginous limbs meet dorsal to the neural canal and failure to do so results in spina bifida.

Two centers of ossification appear and fuse in the centrum in the bony stage (seventh week). One appears in each of the two limbs of the neural arch and unite at the fourth or fifth year. The body of the vertebra is formed from the centrum and the basal part of the neural arch. The neural ossifications fuse posteriorly in the first year and the spinous processes, transverse processes and ribs are formed by outgrowths of cartilage into the septa between the somites. The costal processes fuse with the transverse processes except in the dorsal region where they remain as separate elements.

The atlas represents the completed bow of the first cervical vertebra. Its body fuses with the body of the second to form the odontoid process of the axis. The occipital or posterior part of the skull represents at least three united vertebrae. Very rarely the last of these may partly assume a vertebral form. It is not rare to see the first cervical vertebra partly fused with the occipital bone. This represents a tendency to add a fourth vertebra to the occipital series. In the cervical vertebrae the anterior part of the transverse process represents a costal process, but only in the sixth and seventh is this process formed by a separate ossification center which is usually vestigial and may form a rudimentary or fully developed rib.

Since a vertebra has its own potentiality and may assume the characteristics of the segment above or below it, such irregularities are classed as "normal or functional." During the period of segmentation the embryo may be subjected to injurious conditions and "abnormal or pathological" peculiarities may be produced. Segments may separate irregularly so that ribs or vertebrae become fused, or hemivertebrae occur. Associated anomalies in the other systems are not infrequent. Figure 1 depicts the spinal column and the costal series of a fetus illustrating marked irregularity in segmentation.

ETIOLOGY

A congenital synostosis of the cervical spine (Klippel-Feil syndrome) is therefore probably due to the irregular segmentation of the spine occurring in the early weeks of fetal life. Such disturbances of normal development are not to be regarded as regressive or progressive tendencies in phylogeny, but are rather the result of morbid conditions in the parent interfering with the normal fetal development.

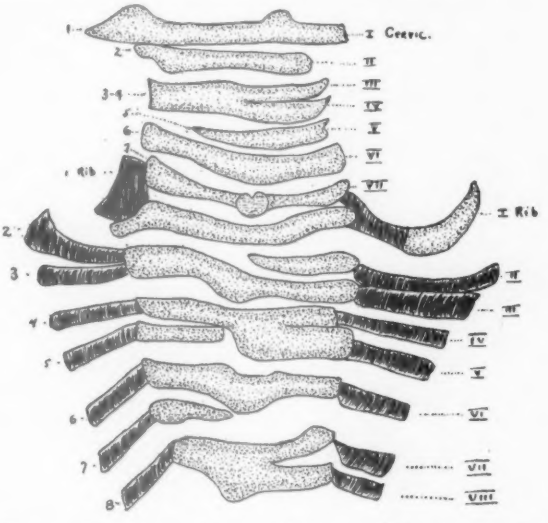

Fig. 1. Cervical and dorsal parts of the spine of a human fetus showing irregularities of segmentation. (Drawn from "Human Embryology and Morphology" by Sir Arthur Keith, page 81, Fig. 74, fifth edition, 1933, by permission of the publishers, William Wood and Company, Baltimore.)

Many other theories have been advanced. Klippel and Feil in 1912 believed the condition due to intrauterine inflammation or trauma. Feil in 1919 expressed belief that a high spina bifida was the original lesion and that pressure and trauma later in fetal life resulted in fusion and malformations. Jaubert de Beaujeu and Bloch[25] believe that hereditary syphilis is a factor. Because nerve lesions are not rare, it has been suggested that the original lesion was in the central nervous system rather than in the skeletal system.

CLINICAL PICTURE

Little has been added to the clinical description of the case originally reported by Klippel and Feil.[28,29] The head in this patient appeared to be resting on the trunk, the thoracic cage rose to the base of the

skull, the hairline was implanted very low, and all movements of the head and neck were greatly restricted. In 1919 Feil[9] outlined the essential characteristics of the syndrome.

Primary characteristics are: (1) Shortness of the neck. The head appears to be directly implanted on the trunk. The neck is broad and the chin approximates and may even rest on the sternum. Occasionally the trapezii stretch winglike from the mastoid processes to the shoulders, suggesting the name of "pterygium colli" or "web neck." (2) Low implantation of the hairline. (3) Limitation of movements of the head and neck. These movements are painless, the deficiency being purely a mechanical one.

Secondary characteristics are: (1) Scoliosis or kyphoscoliosis. (2) Elevation of the scapulae (Sprengel's deformity). (3) Descent of the nipples of the breast. (4) Torticollis of muscular or osseous origin. (5) Disproportion between the length of the extremities and of the trunk giving the patient an almost simian-like appearance. These are the features of the extreme type. The essential characteristics described above need not all be present. They may occur in whole or in part and with varying degrees of intensity.

Defects have been noted in other parts of the body, frequently congenital in type, such as abnormal dentition, cleft palate, facial asymmetry, deformities of the forearm, clubfoot and clubhand, defects of the trapezii and other muscles, and vertebral deformities in the dorsal, lumbar and/or sacral regions. Disturbances in the nervous system are not infrequent. The following associated findings have been reported: Mental weakness, deaf-mutism, spastic quadriplegia (Guillain and Mollaret;[22] Baruch[2]), syringomyelia (Kallius[26]), anesthesias and paresthesias (Roger, Arnaud and Audier[39]), pseudomyopathy (Sicard and Lermoyez), thenar and hypothenar atrophy (Kallius[26]), cervical spasm with difficulty in breathing and swallowing (Bauman[3]), hereditary ataxia of the Marie type or Friedrich's ataxia (Mattirolo and Bertolotti[30]), and mirror movements (Bauman[3]; Willard and Nicholson[44]).

The spinal anomaly is always present at birth although it may not be recognized at the time. If the infant survives, the deformity is compatible with life. Death in adult life is frequently due to an intercurrent acute infection. A familial tendency is noted. Feil reported the syndrome in father and son, Bar[1] in brother and sister, and Kallius[26] in father and daughter, and Sicard and Lermoyez[2] in a mother and three children.

PATHOLOGICAL ANATOMY

Feil described specimens which on examination showed (1) a reduction in the number of cervical vertebrae which were fused in whole or in part; (2) the existence of a superior cervical spina bifida; and (3) elevation of the thoracic cage with formation of a cervical thorax which was more or less developed.

Post-mortem specimens reported by Mitchell,[33] Klippel and Feil,[28,29] Feller and Sternberg,[17] and others, reveal platyspondyly,[5] cervical and fused ribs, congenital elevation of the scapula with or without bony attachment, and deformity of the dorsal, lumbar and sacral segments. In many cases a large triangular opening (spina bifida) is present in the posterior part of the cervical spine and may extend from the cranium to the thoracic cage. The atlas is often fused to the occipital bone and a basilar or craniocervical kyphosis is almost always present. A synostosis between the atlas and odontoid process is a less common finding, while fusion between the second and third cervical segments or of the vertebrae below are more frequent. Anomalous defects such as a supernumerary lobe of the lung, patent foramen ovale and an interventricular septum have been noted.

ROENTGENOGRAPHIC FINDINGS

The positions best demonstrating the cervical anomalies on roentgen examination were studied by Feil.[13] He recom-

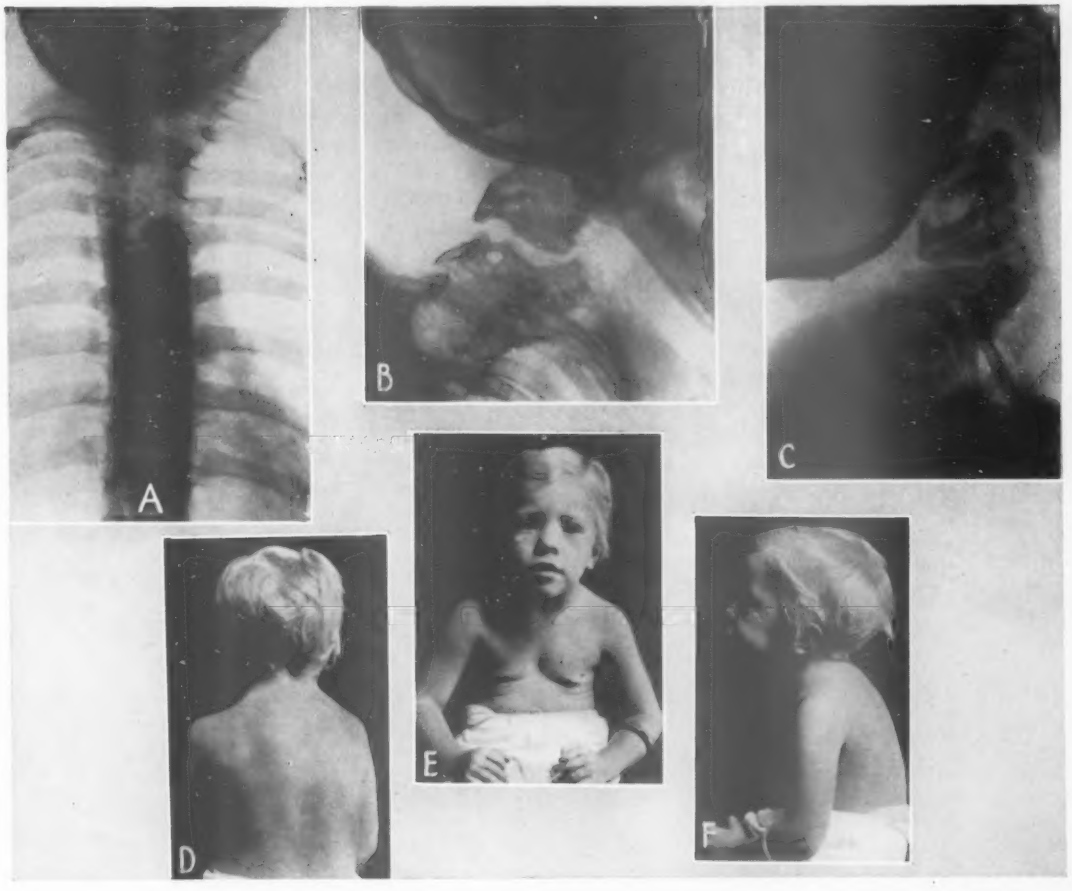

Fig. 2 Case 1. *A*, shows the ascent of the thorax, bilateral cervical ribs, occult spina bifida of the fifth and sixth thoracic segments. *B*, shows the fused upper cervical mass separated from the cervicothoracic segments by a distinct hiatus. *C*, shows a flattening of the cervical curve at its upper portion and acutely angulated forward inferiorly. There are apparently only three cervical spinous processes. The bodies and spinous processes of the cervicothoracic area are fused. Platyspondyly of the cervical segments is noted. *D*, *E*, *F*, note the short, broad neck, low hair line, round back, the slight tilt of the head to the left and the low nipple line.

mended the right and left oblique anterior, anteroposterior and lateral views. Roentgenograms must be made through the open mouth and by axial projections from the base of the skull in order to secure images of the atlas and axis and their articulations. The findings corroborate and, in the absence of typical clinical manifestations, make the diagnosis.

TREATMENT AND PROGNOSIS

There is no therapy for the cervical deformity itself. The condition, if the infant survives, is compatible with life. Massage and stretching may be utilized. Heidecker[23] reports improvement in mobility after gymnastic exercises. Thomson[43] obtained improvement in a patient by hyperextending the spine on a frame for one-half hour twice a day. Ryerson[40] divided the outer portions of winged trapezii in one patient with good cosmetic effect. Associated deformities such as scoliosis, torticollis, clubfoot and clubhand should be corrected.

CASE REPORTS

Five case reports are herewith presented, including 3 typical cases of Klippel-Feil syndrome and 2 cases of congenital synostosis of the cervical vertebrae. Embryo-

logically the latter may well be interpreted as representing intermediary or interrupted phases of the syndrome, which in the absence of a typical clinical picture might well have remained undiagnosed except for coincidental roentgen findings.

CASE I. J. S., female, aged four, was first examined on May 27, 1935. The family history was negative. The deformity had been noted since birth. She presented a short, broad neck, a low hair line, a round back, and a very slight tilt of the head to the left, with a descent of the nipple line (Fig. 2*D*, *E*, *F*). Dimpling at the lower end of the spine suggested a spina bifida sacralis. A pectus excavatus was noted. The lower extremities were mildly spastic and the patellar reflexes were exaggerated.

Roentgenograms made on June 10, 1935, showed on the anteroposterior view (Fig. 2*A*) the ascent of the thorax, cervical ribs bilaterally, and an occult spina bifida of the fifth and sixth thoracic segments, with an apparent fusion of the spine above this area associated with a scoliosis to the left. In the lateral view (Fig. 2*C*) the cervical spine was flat at its upper portion and acutely angulated forward inferiorly, and associated with an exaggerated dorsal kyphosis. There were apparently only three cervical spinous processes. There was a fusion of the bodies and spinous processes of the lower cervical upper thoracic vertebrae. Platyspondyly of all the cervical segments was noted. The oblique view (Fig. 2*B*) showed the fused upper cervical mass separated from the lower cervicothoracic segments by a distinct hiatus.

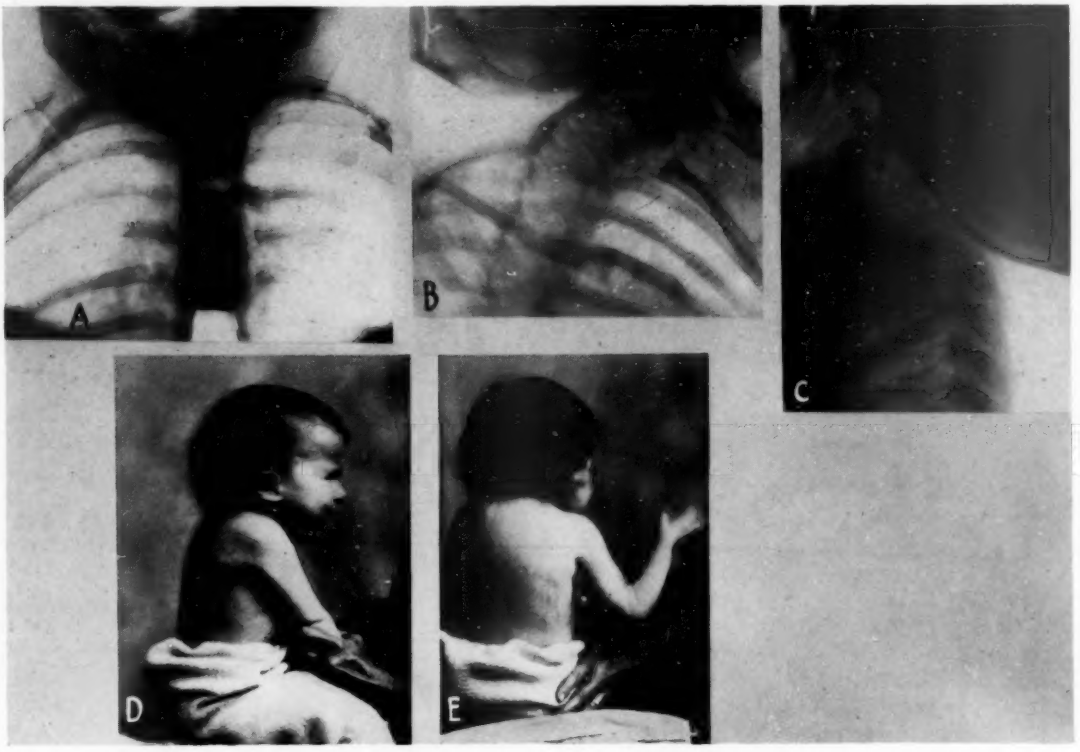

FIG. 3. Case II. *A*, shows a slight right torticollis; a loss of definition of the upper thoracic spine, platyspondyly and an occult spina bifida. *B* and *C*, show irregular segmentation, fusion, and flattening of the vertebral bodies, and an ascent of the thorax. *D* and *E*, show the characteristic low hair line, round back and short, broad neck. The head is enlarged and seems to rest on the shoulders.

CASE II. M. M., female, aged ten months, was examined on September 23, 1935. The family history was negative. The deformities present had existed since birth. The patient had the characteristic low hair line, round back and short, broad neck of the Klippel-Feil syndrome (Fig. 3*D*, *E*). The head seemed to rest on the shoulders so that the interval between the mastoid processes and the shoulders was but

one finger-breadth distance. The head was enlarged. She was mentally deficient and unable to sit without support. Associated were bilateral spastic talipes equinus deformities and a double internal strabismus.

Roentgenograms made on October 6, 1936, revealed, on the anteroposterior view (Fig. 3*A*) a slight right-sided torticollis, a loss of definition of the upper dorsal spine, platyspondyly and an occult spina bifida. The oblique and lateral views (Fig. 3*B* and *C*) showed irregular segmentation, fusion and flattening of the vertebral bodies, with ascent of the thorax towards the base of the skull.

Case III. R. K., male, aged seven (reported through the courtesy of Dr. Harry Subin, Atlantic City). Unfortunately no detailed clinical records of this case were to be had, but from the roentgen examination a rather typical picture may readily be presumed. Roentgenograms made in October, 1936 showed on the lateral view (Fig. 4*A*) almost complete fusion of the entire cervical spine with shortening of the neck and with platyspondyly especially of the lower segments. An anteroposterior view, not illustrated, evidenced a high spina bifida dorsalis.

Case IV. B. H., male, aged forty-eight, whose chief complaints were that of chronic low back disability and a left sciatic neuralgia, showed on examination slight limitation of all the movements of the head and neck associated with slight discomfort referred to the cervicothoracic region. No abnormality or deformity could be observed clinically, nor was there a preceding history of injury or infection.

Roentgenograms taken in November, 1936 (Fig. 4*B*, *C*) showed incomplete fusion between the second and third, and third and fourth cervical segments and platyspondyly in the lower vertebrae. Additional findings, not illustrated, were spina bifida occulta of the first sacral vertebra, a bifid spinous process of the second lumbar vertebra, and anterior wedging of the upper dorsal segments associated with an exaggerated dorsal kyphosis.

Case V. E. B., female, aged twenty-nine, was referred to the senior author by Dr. Jackson Taylor of Coatesville, Pa. She never noted any deformity or discomfort of the neck until September, 1936, when a falling object struck her on the back of the neck. A painful right torticollis deformity resulted, associated with spasm

Fig. 4. *A*, Case III, shows almost complete fusion of the entire cervical spine, a shortening of the neck and platyspondyly. *B* and *C*, Case IV, show incomplete fusion between the second and third, and the third and fourth cervical segments and platyspondyly. *D* and *E*, Case V, reveal almost complete fusion of the third and fourth cervical vertebrae.

of the cervical muscles, limitation and guarding of the motions of the neck in all directions, actively and passively, and numbness in the right shoulder. She was partially relieved by traction and a Thomas collar. Temporary relief (for one month) followed immobilization in a Calot jacket for a period of three months.

Roentgenographic studies made on November 27, 1936 (Fig. 4*D*, *E*) revealed almost complete fusion of the third and fourth cervical vertebrae with no other deformity and without evidence of fracture or disease.

SUMMARY

The embryological considerations, the clinical aspects, the the pathological anatomy of the syndrome of congenital synostosis of the cervical spine (Klippel-Feil syndrome) have been described in detail. Three typical cases of the syndrome, two of these with neurological findings, are reported. Two cases of synostosis of the cervical vertebrae are included, as these represent intermediary phases of the cervical maldevelopment. The existence of such congenital anomalies becomes of paramount importance as potential areas of lowered resistance.

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OSTEOPETROSIS ASSOCIATED WITH HODGKIN'S DISEASE

REVIEW OF THE LITERATURE AND REPORT OF CASE*

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IN 1904 Albers-Schönberg[1] described a rare disease characterized by generalized osteosclerosis, anemia, and enlargement of the liver, spleen and lymph nodes. Because the normal trabecular structure of the bones was obliterated and replaced by a generalized homogeneous density, not unlike marble in appearance, he attached the name "marble bones" to this condition. In 1922 Davis[5] reported the first case in America; and in 1930 Pirie[14] in presenting a series of 3 cases occurring in one family described the development of these interesting bone changes. He discovered that the bones, while exhibiting a marked increase in density, yielded readily to instrumentation and were extremely brittle. From these findings Pirie concluded that the calcium carbonate deposited in the bones resembled chalk rather than marble and he suggested the name "chalky bones." Karsner[8a] suggested "osteopetrosis" as a name for the condition. It is interesting to note that the brittleness of the bones gives rise to the symptom most commonly associated with the disease, and that it is this symptom, namely multiple fractures, that most often brings the patient to the physician. Since the original presentation by Albers-Schönberg 90 cases have been recorded in the literature of which our case represents the first in which the condition was associated with Hodgkin's disease. Since enlargement of the liver, spleen and lymph nodes occurs almost invariably in Albers-Schönberg's disease, these findings were at first interpreted as a feature of the latter condition. Histological sections, however, revealed the undoubted presence of Hodgkin's disease as well, its authenticity being verified by various competent pathologists. A case of osteopetrosis complicated by osteogenic sarcoma was reported by Kerr[9] in 1936.

RELATIONSHIP TO FLUORINE POISONING

In 1936 Spéder,[15] while studying a case of Albers-Schönberg's disease in a Moroccan native, was struck by the resemblance in the bone changes he found in this condition and those he had previously noted in animals suffering from a disease known as "darmous." The latter condition occurs in animals living in phosphate zones where the drinking water besides containing phosphates is known to contain small quantities of fluorides as well. The disease has been produced in experimental animals by including small amounts of fluorides with their diets over a long period of time. Spéder had noted that Moroccan natives living in the phosphate zones frequently suffered from malformation of the mandible, disturbances in dentition, and even osteomyelitis of the jaw, all of which are commonly found in Albers-Schönberg's disease. Accordingly he made roentgenographic studies of the skeleton in 6 such natives who exhibited marked dental disturbances, and in all findings resembling those of Albers-Schönberg's disease were present. Spéder concluded from these observations that the latter condition was caused principally by chronic fluoride poisoning, and was a relatively common rather than a rare disease.[16]

That chronic ingestion of fluorides will produce generalized osteosclerosis has long been known. In 1891 Brandl and Tappeiner[3] reported the findings noted in a dog fed 402.9 grams of sodium fluoride over a period of twenty-one months. The dog died accidentally of illuminating gas poisoning and the autopsy, while revealing no change

* From the Tumor Clinic and Research Unit, Veterans' Administration Facility, Hines, Illinois. Published with the permission of the Medical Director, Veterans' Administration, who assumes no responsibility for the opinions expressed by the authors.
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in the blood or liver, showed numerous changes in the bones. There was generalized involvement of the skeletal structures. The bones were chalky white in appearance, hard and brittle. Histological studies revealed the bone structure to be intact. The haversian canals, however, were filled with crystals of calcium fluoride. Similar results were reported subsequently by Stanton and Kahn[17] and others.

DeEds[6] demonstrated further that dogs fed on diets containing fluorides showed not only the bone changes noted above but dental defects, anemia and cachexia as well. These symptoms are commonly found in Albers-Schönberg's disease. DeEds expressed the opinion that in humans ingested fluorides were only partially eliminated, a certain portion being fixed as calcium fluoride and deposited in the bones and teeth.

Bishop[2] made careful roentgenological studies of the bone changes in a human being suffering from chronic fluoride poisoning. The bones showed a generalized increased density without alteration of their normal architecture. The increased calcification extended, however, to the ligamentous attachments. The earliest changes were found in the spine and pelvis, following which the bones of the extremities became involved. The margins of the bones became indistinct in outline due to extension of the calcification to adjacent soft tissue structures. Osteophyte formation, calcification of the intervertebral ligaments, roughening of the margins of the pelvis, and extension of bony spicules from the pubes and ischia into the soft tissues were noted. Flemming-Møller and Gudjonsson[7] noted increased calcification of the costal cartilages as well. Neither the latter authors nor Bishop mention the possibility of an etiological relationship between chronic fluoride poisoning and Albers-Schönberg's disease.[15] The roentgenographic findings in the latter condition resemble those noted in chronic fluoride poisoning in many respects. There is a generalized increase in density affecting the greater portion, if not the entire skeleton. The bones first involved are the spine and pelvis; later the proximal ends of the humeri, the distal ends of the tibiae and fibulae, the base of the skull, and the posterior clinoids are involved. Eventually the remainder of the skeleton may become involved. The trabeculae are partially or completely obliterated. The medullary canal similarly is obliterated, either in part or completely, so that the bones exhibit an amorphous, homogeneous density delimited by their contours. Other findings in this condition include stratification of the bones particularly in the extremities, so that bands of greater and lesser density may be seen running parallel to the epiphyseal lines. This process, while more common at the ends of the bones, may extend into the shafts and may even involve the entire bone. The posterior clinoids frequently show club-like thickening. The ends of the long bones may at times exhibit symmetrical widening. The extension of calcification into ligaments and other adjacent soft tissue structures has not been noted by the authors.

Among the concomitant roentgenological findings are multiple fractures, generally well healed by abundant callous formation, thickening of the periosteum and deformities of the mandibles and maxillae. Not infrequently a superimposed suppurative process is found involving the mandibles, maxillae, or more rarely, the long bones. Rickets is occasionally found as an associated condition. Hydrocephalus, epiphyseal deformities, evidences of physical underdevelopment are among the more common associated findings; while disturbances in dentition are an almost universal manifestation.[18] Due to the overgrowth of the cranial bones, the foramina of the skull may become narrowed, resulting in pressure atrophy of the nerves emerging through these foramina. The optic nerve is most frequently involved, resulting in restriction of the visual fields; less commonly, disturbances in hearing result from pressure upon the auditory nerves.

PATHOLOGY

The pathological findings are confined chiefly to the bones, liver, spleen and

lymph nodes. There is an overgrowth of the cortex and spongiosa of the bone at the expense of blood vessels, fatty and myeloid tissues.[12] The spongiosa may become so dense that it is indistinguishable from the cortex. The medullary canal is encroached upon and may become completely obliterated.[10,11,12] The individual trabeculae are thickened and greatly increased in number. By means of polarized light the lamellar structures are found to be distorted and the haversian canals malformed.[11,19] The liver, spleen and lymph nodes are generally enlarged and fibrotic.

HISTOLOGY

Histological studies reveal an abnormal amount of osteoid tissue in the bones. (Even the medullary cavity may contain large amounts of osteoid tissue.) Osteoblasts are present in abundance throughout the cortex and spongiosa.[8,13,19] In some areas osteoclasts may be seen actively producing lacunar absorption.[4,10] This process, however, is soon replaced by renewed osteoblastic activity with a new laying down of dense irregular trabeculae.[11,19] It is apparent throughout that osteoblastic activity far exceeds osteoclasis and bone formation is in excess of resorption.[19]

The bone marrow is replaced by fibrous tissue in the meshes of which scattered islands of hematogenic elements are noted. Excessive fibrosis is noted in the liver, spleen and lymph nodes and hemopoiesis is depressed.[4,10,11,12,19]

The histogenesis of the abnormal bone structure has been carefully studied by Laubmann[11] and Zwerg and Laubmann.[19] The precartilaginous connective tissue lays down a cartilaginous ground substance. An abundance of cartilaginous cell capsule is noted in which is deposited a relatively large amount of calcium. Primary trabeculae are formed by the numerous, highly activated osteoblasts, but resorption of the primary trabeculae is delayed. Secondary trabeculae cannot thus be formed. There is evidently a disturbance in the endosteal and endochondral metabolism of bone due to the action of some unknown primary osteoblastic agent. Consequently, bone formation is far in excess of bone resorption.

BLOOD FINDINGS

The blood picture presents evidence of the disturbances in hemopoiesis. There is generally a severe anemia of the hypochromic type. In adults the anemia may be mild in degree and even absent. Hyperchromic anemia is occasionally found. The degree of anemia varies considerably but there is no necessary relationship between its severity and the extent of bone involvement.[12] It is always marked before death. In the blood smear immature red blood cells (chiefly normoblasts with an occasional megaloblast) are found.[12] The platelet count is often low. The leukocyte count is high in children but may be normal in adults. In the terminal stage a blood picture resembling leukemia may develop.

PROGNOSIS

The course of the disease varies considerably with the age of the patient. In infants and young children the symptoms are, as a rule, severe. The anemia is generally marked and the prognosis is bad, particularly when hydrocephalus or a leukemic blood picture is found. In adults the disease is more benign in character; indeed it may be in an arrested state. The blood picture may be entirely normal and symptoms may be absent. The tendency to fracture with relatively little trauma brings the patient to the physician and the true nature of the disease, which would otherwise have gone undiscovered, is revealed after a roentgenogram for a supposedly simple fracture shows extensive osteosclerosis of the bone. The disease may exhibit stages in which progression and arrest alternate, accounting, perhaps, for the alternating bands of greater and lesser density sometimes found in the long bones. In the majority of cases the disease is progressive in character and death results either from progressive anemia, intercurrent infection or cachexia resulting from extensive suppurative disease of the bones.

TREATMENT

There is no specific therapy for an uncomplicated case of osteopetrosis. The anemia may be treated by the use of various iron and liver preparations available. The general health of the patient should be maintained as well as possible and precautions taken against trauma and secondary infections. Calcium and cod liver oil should not be used.

ETIOLOGY

The etiology of osteopetrosis is unknown. There may be a variety of factors responsible for its production.[12] The relatively benign course of the disease in adults as compared to infants and young children suggests the possibility of a different set of operative factors in the former group. The causes of this disease may be similar in some respects to those producing other diseases of the hemopoietic system. Any attempt to arrive at an ultimate cause must of necessity properly evaluate those factors which are most commonly found associated with the condition. Those which are known and which were recognized soon after the first description of the disease are: the familial tendencies; the high incidence in parents and grandparents of patients suffering from the disease; and the predominance of the condition in infants and young children. Albers-Schönberg recognized the familial tendencies. Subsequently other investigators demonstrated this conclusively. McPeak[13] reported 8 cases occurring in three generations of one family. Pirie,[14] d'Istria,[8] and others, similarly have reported cases occurring in more than one member of the same family. These factors strongly favor the belief that the disease results from some defect in the primitive germ plasm. Kudrjawtzewa[10] believed the disease was caused by a mutation of the germ plasm, resulting in a dyscrasia of that portion of the mesenchyme which in its evolution is destined to form the hemopoietic system. The high incidence among relatives speaks for a hereditary factor which is carried as a mendelian recessive and is therefore accentuated by inbreeding. The preponderance of cases occurring in infants and young children gives added weight to the latter contention.

While it must be admitted that generalized osteosclerosis may be produced by a variety of causes, not all cases of osteosclerosis are to be considered Albers-Schönberg's disease. Chronic fluorine poisoning doubtless will produce a generalized osteosclerosis, but the extension of calcification to the soft tissues, ligaments, and other periosseous structures in the latter condition, as described by Bishop,[2] Flemming-Møller,[7] and others seems to differentiate this condition from true Albers-Schönberg's disease. Moreover, the presence of calcium fluoride crystals in the haversian canals in the former case with practically no disturbance in the architecture of the bone[6] is at marked variance with the histological picture described in Albers-Schönberg's disease.[19] Generalized osteosclerosis has been produced in rats by Selye with concentrated parathormone extracts. Phosphorous poisoning frequently produces bone changes which simulate those in Albers-Schönberg's disease: notably necrosis and osteomyelitis of the mandible, disturbances in dentition, and even stratification of the long bones.

Pirie believed that a generalized epiphysitis was responsible for the bone changes found in Albers-Schönberg's disease. The histological picture does not, however, bear out such a contention. Moreover, as McPeak has pointed out, the relative absence of general symptoms in this condition is at variance with what one might expect in so widespread an epiphysitis. Then, too, in the bones of the hands and feet, which have only one epiphysis, the disease may be found simultaneously at both ends. These considerations, along with the concomitant enlargement of the liver, spleen, and lymph nodes, an enlargement which, as Clairmont and Schinz[4] and others pointed out, is not a compensatory phenomenon, but rather a developmental defect just as the changes in the bones are, militates against Pirie's contention.

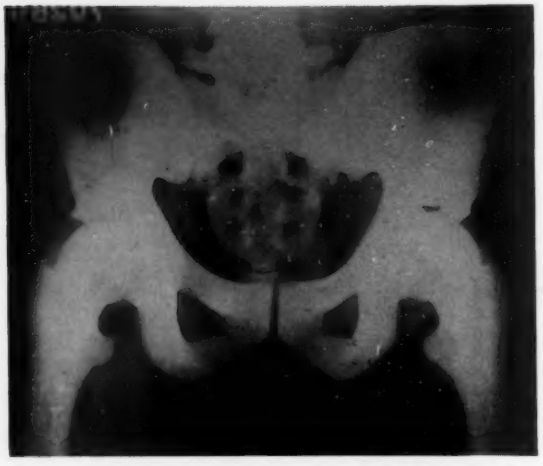

FIG. 1. Film of pelvis showing typical appearance of osteopetrosis.

There appears to be no definite relationship to endocrine disturbance. Pehu and his coworkers found a parathyroid tumor in their case, but this doubtless was a coincidental finding as Hodgkin's disease was in our case. In none of the other cases reported was there any notable endocrine disturbance.

CASE REPORT

The patient, A. M. R., a white male, aged forty-one, was admitted to the Edward Hines, Jr. Hospital on May 19, 1937. His chief complaint was pain and swelling in the right ankle associated with large nodes in the right inguinal region.

Family History. Father was born in Iowa, living, aged eighty-six, health good. Mother was born in Missouri, died in 1927, at the age of seventy-one, of heart disease. Two brothers living and well. Two brothers dead, one killed accidentally, and one died of "stomach trouble." Two sisters living and well. Two sisters dead, causes unknown. No history of fractures.

Personal History. Had measles, mumps, whooping cough, and smallpox in childhood. No other illnesses except present one. Fractured his left arm falling off a ladder in 1930. This fall was of sufficient force to produce a fracture in a normal bone. Smokes one package of cigarettes daily; drinks beer and whiskey occasionally but not to excess. Has had no operations. Denies venereal infection. Married and has three children all of whom are in good health. No history of fractures. The patient has lived near Eldon, Missouri, all his life.

Present Illness. Patient states that he was well until May, 1938, at which time he first noticed swelling and pain in his right ankle. At the same time enlarged nodes in both inguinal and axillary regions appeared. Loss of 12 pounds in weight during past year. Also gradual loss of strength. Inventory by systems negative.

Laboratory Examination. Wassermann and Kahn reactions negative. Blood count: red blood cells, 4,030,000; white blood cells, 10,000; hemoglobin, 80 per cent. Differential count: polymorphonuclear leukocytes 68 per cent; lymphocytes 28 per cent; monocytes 4 per cent. Blood chemistry: calcium 12 mg. per 100 cc.; inorganic phosphorus 2.58 mg. per 100 cc. Histological report: Microscopical examination of tissue removed from the left inguinal region reveals a diagnosis of Hodgkin's disease. This was confirmed by several other pathologists.

Radiation Therapy. Patient received a total of 600 roentgens to the right side of the neck;

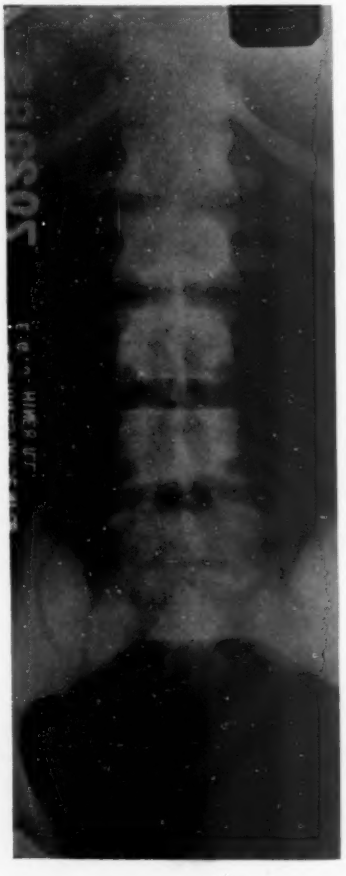

FIG. 2. Anteroposterior film of lumbar vertebrae showing them to be dense and with loss of usual detail.

600 r to the left side of the neck; 600 r to the right axilla and also 600 r to the left axilla; 1,000 r to the right groin and 1,000 r to the left groin. Factors of treatment: 200 kv., 0.5 mm. Cu and 2 mm. Al, 50 cm. target-skin distance and 20 ma. The patient improved considerably and the lymph nodes regressed. He was discharged on July 23, 1937.

He was re-admitted on February 24, 1938, because of loss of strength, enlarged inguinal lymph nodes, and edema of the scrotum, penis, and ankles. Roentgenograms were taken of his entire skeleton and revealed the same changes as on his previous admission. Laboratory findings were essentially the same as before with the exception of urinary findings suggestive of nephritis. Bence-Jones protein was not found in the urine on either admission. Blood calcium and phosphorus were also normal. There was a mild secondary anemia on this admission. He received radiation therapy to the right and left groins and was discharged improved on April 13, 1938.

Physical examination reveals an ambulant white male, well developed and nourished, appearing chronically ill. The lymph nodes in the neck, axillae, and groins, are enlarged. The nodes are firm in consistency and not tender on palpation. Both ankles and feet are edematous. There is marked edema of the penis and scrotum secondary to lymphatic obstruction. The liver and spleen are enlarged. The left elbow is partially ankylosed as a result of an old fracture near the elbow joint. The patient also had an eczematoid dermatitis on admission which is occasionally seen accompanying Hodgkin's disease. The visual fields and eyegrounds are normal. The teeth are in poor condition. The remainder of the physical examination is essentially negative.

Roentgen Examination. The bones of the skull and face show a slightly uniform increase in density. The sella turcica is normal in size and structure but is denser than normal. There is no evidence of intracranial pressure. Roentgen examination of the chest reveals the heart and lung fields to be normal; however, the entire bony framework of the chest has an ivory ap-

Fig. 3. Lateral film of the foot showing marked increase in density of the bony structures.

Fig. 4. Bones of the wrist and hand are also involved.

pearance. The cervical, thoracic and lumbar vertebrae are quite dense. The bones of the pelvis, sacrum and coccyx are all involved. All long bones show a homogeneous increase in density with loss of detail and obliteration of the medullary spaces. The carpals, metacarpals tarsals, metatarsals, and phalanges all show marked involvement.

SUMMARY

1. A case of Albers-Schönberg's disease (marble bones) associated with Hodgkin's disease is presented. This is the only case found in the literature.

2. The relationship of Albers-Schönberg's disease to fluorine intoxication is discussed. It is the belief of the authors that the type of osteosclerosis produced by such intoxication differs from true Albers-Schönberg's disease in that the excessive calcification in the former condition frequently extends into the adjacent soft tissue structures; such is not the case in the latter disease. Histological studies, furthermore, show well defined differential features in the two conditions.

3. While the etiology of Albers-Schönberg's disease is unknown, the high incidence in parents and grandparents of patients suffering from the disease, the greater incidence in infants and young children and the frequent occurrence in more than one member of a family point to a hereditary defect in the germ plasm carried as a mendelian recessive factor and accentuated by imbreeding. This defect apparently results in a disturbance in metabolism which affects the entire hemopoietic system. There is excessive osteoblastic activity involving the greater portion of, if not the entire skeleton; and an associated fibrosis and enlargement of liver, spleen and lymph nodes. Hemopoiesis is generally depressed.

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Vol. 43, No. 1

STUDIES OF HUMAN NERVOUS AND RELATED TISSUE BY THE ROENTGEN-RAY DIFFRACTION METHOD AND THE PETROGRAPHIC MICROSCOPE*

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THE problem of applying roentgen-ray diffraction measurements to the study of materials met in biology and medicine is still new and we are somewhat in the position of the early histologists who could make only fundamental observations, as contrasted with the modern pathologists who, in practically every instance, give a complete diagnosis. A number of investigators[1,2,3,4] have begun the study of tissue and the nervous system in lower animals by the use of roentgen-ray diffraction methods. The most recent as well as the most extensive work has been done by Clark and his associates.[4,5,6,7] Up to the present time, however, little work has been done on human nervous tissue.

In this study we are investigating the fine structure of the human brain, and the vagus and sympathetic nerves, together with some of the related structures, such as dura and some tumors.

The experimental diffraction work was done with a Philips Metalix copper target tube. Three and 5 cm. distances were used. All of the patterns reproduced for illustration, however, were taken at 5 cm.

As is well known, this method of investigation can be used to gain direct information about the size, composition, and arrangement of structural elements which lie beyond the range of the ordinary microscope. Much work has been done on the structure of natural fibers such as silk, wool,[9] and cotton.[10] It was found in all instances that the large organic molecules and micelles were arranged or "oriented" so that their long axis was parallel to the length of the fiber, that is oriented along the line of a definite directional stress.

With this in mind, it was hoped that the same method might be applied to the study of nervous and related tissue and in this way we could learn more of their actual submicroscopic structure, thus obtaining a better understanding of the individual characteristics of different types of structure in both their normal and pathological states.

Early in this investigation, it was found that some types of nerve structures showed a high degree of orientation while others did not.

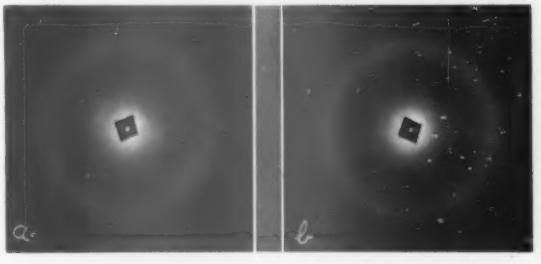

FIG. 1. *a*, vagus nerve, longitudinal section; *b*, submaxillary ganglion.

In diffraction patterns, molecular orientation along a given axis of the sample may be shown by a sharpening and an intensification of the circles of the pattern into arcs, the sharper the arc the greater the degree of orientation. This is illustrated by Figure 1*a* which is a longitudinal section of the adult vagus nerve. The more sharply defined arcs appear at the longer spacings of 12.3 Å. There is some orientation shown by the faint arc at 2.86 Å. In contrast, Figure 1*b* is a longitudinal section of the adult human submaxillary ganglion from the same individual and treated in the same manner, but showing no orientation.

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Instead, the spacing, which is divided into arcs in the vagus nerve and corresponds to 12.3 Å., is shown as a continuous ring. In the nerve trunks in general the property of orientation can be noticed in those which have a highly specialized directional function, but, as would be expected, is absent in both the gray and the white matter of the brain and in the ganglia so far investigated, in both the sensory-motor and the sympathetic systems. It is possible that certain organized tracts through the brain are oriented, but this has not been shown by our diffraction patterns. Photographs taken in polarized light, as shown later, do, however, show evidence of whole groups or tracts of nerve fibers in the white matter (Fig. 8).

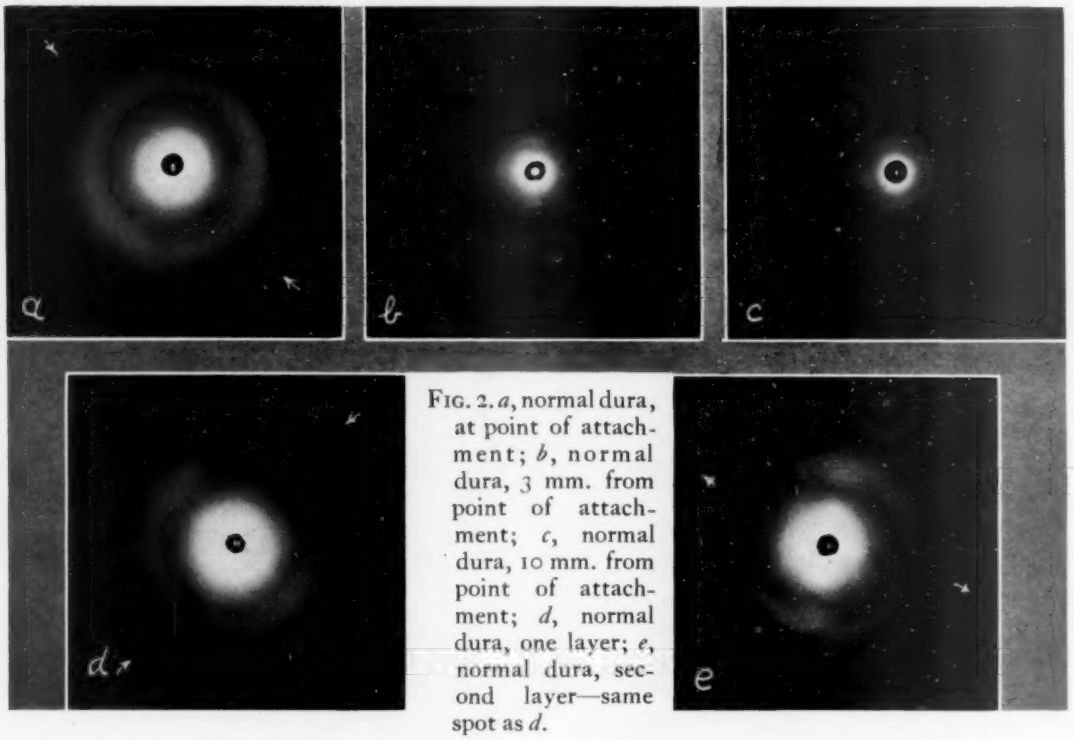

FIG. 2. *a*, normal dura, at point of attachment; *b*, normal dura, 3 mm. from point of attachment; *c*, normal dura, 10 mm. from point of attachment; *d*, normal dura, one layer; *e*, normal dura, second layer—same spot as *d*.

This property of orientation is also well illustrated by the dura. A study was started to map out the surface of the dura along with the underlying tissue in order to determine the degree and direction of orientation with respect to normal points of stress and normal interfering structures. It was hoped that in this manner an index to the origin of meningiomas might be obtained since Cushing and Eisenhardt,[10] as well as other authorities, have shown that there are such definite areas favored for this type of tumor. This analysis is not yet completed, and will necessarily have to continue over a long period of time. Certain results have been established and will be discussed in the following.

A narrow strip of whole dura was taken in the parietal region about 3 cm. below the midline, beginning at a point of attachment and extending back for a distance of 2 cm. Figure 2*a* is the diffraction pattern taken directly on the point of attachment. It shows the beginning of directional orientation, and a general circular arrangement of fibers, such as would be expected in order to maintain good distribution of stress at this point. Figure 2*b* is taken 3 mm. away from the point and shows a well organized structure with a high degree of orientation. Figure 2*c* was 10 mm. from the point of attachment and shows a very well defined fiber axis in two directions at 90° to each other. The three patterns show

that the basic idea being studied, orientation vs. strength required by the tissue to withstand directional stress, is substantially correct. It also emphasizes the necessity of studying the periosteal layer separately from the dura proper. Figures 2*d* and 2*e* show precisely the same spot on these two layers, separated and mounted on the diffraction apparatus at exactly the same angle with respect to the beam. It is seen by the fact that the inner arcs of the two layers are approximately 90° to each other that these two layers are each highly oriented along a fiber axis of their own, and the two axes lie in a plane at an angle of approximately 90° to each other. It is also shown that these two layers have a highly organized structure of their own and that the axes of the two layers of the dura parallel or diverge according to their separate functions and point of attachment. This same arrangement is also shown by the microscopic slides and will be discussed later (Fig. 8). This type of molecular alignment has been shown to exist in other normal biological material such as teeth, bones and white connective tissue—all structures which in their normal function have to withstand directional mechanical stress. In any animal tissue which normally shows orientation, it would seem that the lack of this orientation is definite evidence of some sort of pathology.

Since the untreated cerebral tissue and the pathological material failed to give any very distinct differences, it was thought advisable to try various other methods of attack such as different methods of drying, some chemical reactions, and the use of various solvents.

The drying experiments were tried first. Diffraction patterns of the fresh undried normal adult brain, either white or gray matter had shown only two diffuse bands, ± 4.64 and ± 12.0 Å. The outer band divides into a diffuse band at ± 4.64 Å, and a broad line at 4.24 Å, upon fixing the tissue in formaldehyde. When the tissue was dehydrated in acetone, these lines sharpened and separated so that more accurate measurements could be made. A sharp band is then found at 4.18 Å with a somewhat more diffuse band at 4.64 Å, as before. Under these conditions the inner pattern is still too diffuse to allow accurate measurements of long spacings. Acetone drying for a period of one week causes further sharpening of these lines and the appearance of a line about 11.03 Å. Hardening the brain by preserving it in formalin for a long period of time does not give a more complete set of diffraction lines. Under these conditions no difference can be found between the gray and the white matter of normal brain. If, however, thin sections of brain material are prepared and dried very slowly over calcium chloride or with acetone over a period of twenty days or longer, even clearer and sharper patterns are produced. Under these conditions a difference can be demonstrated between the gray and the white matter of the cerebrum. Figure 3*a* shows a characteristic pattern of gray matter and

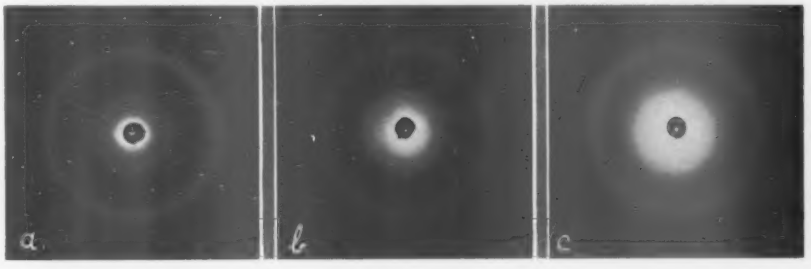

Fig. 3. *a*, cerebral gray matter dried over $CaCl_2$; *b*, cerebral white matter dried over $CaCl_2$; *c*, meningioma dried over $CaCl_2$.

Figure 3*b* that of white matter. Note that the gray matter shows a less hazy ring in the center at about 9.72 Å—one which has a definite circumference.

Figure 3*c* shows the pattern from a meningioma which has also been dried over calcium chloride. Note that this pattern has the characteristic protein ring (±4.7 Å) of both the cerebral matter and the dura, but lacks the orientation of the dura, and the 4.2 spacing of the brain tissue is very weak. Table 1 gives all spacings for these dried tissues as well as those for the nerves and dura which have been referred to previously.

Following the drying experiments addition reactions were used. Various metallic salts, acids and bases were used but they have all been generally unsuccessful. Mild bases are the only chemicals so far tried that offer any encouragement.

In the presence of such complex mixtures as brain or tumor substance, one naturally tries to arrive at a differentiation by appropriate chemical or physical separation of components. In this case serial extractions were run with organic solvents, and the parts extracted by these solvents analyzed separately.

The solvents used were suggested by the work as reported by Bodansky,[11] Schmitt, Bear and Clark,[4] and Page.[12] Of the various solvents used, extractions made with acetone followed by a mixture of 5 per cent alcohol and 95 per cent benzene proved to be the most useful. The following comments will be concerned with the tissue after extraction and the solutions from the acetone or the benzene-alcohol mixture. All of the tissues used had been preserved for several weeks in formalin. The specimens were cut into thin slices and extracted in a modified Soxhlet apparatus for a period of twenty-four hours with acetone. The acetone was then replaced by the benzene-alcohol mixture and extraction continued for another twenty-four hours. The solutions were then evaporated, keeping the temperature always below 90°. The sticky residues were then mounted in small loops of nickel wire and the diffraction patterns taken. Figure 4 shows patterns

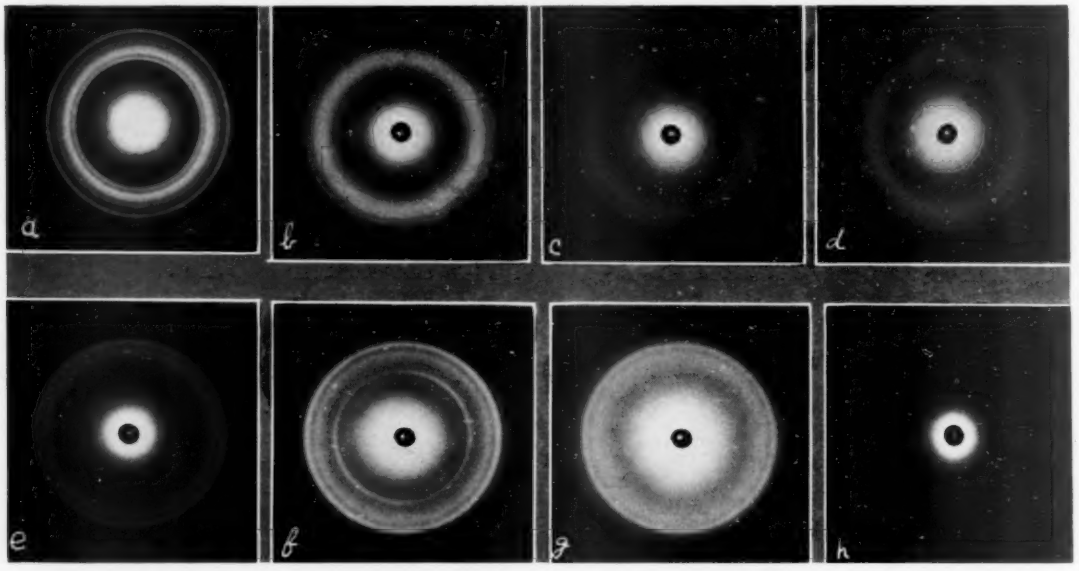

FIG. 4. *a*, acetone extract from normal cerebral tissue; *b*, acetone extract from normal dura; *c*, acetone extract from a chromophobe adenoma; *d*, acetone extract from a meningioma; *e*, benzene-alcohol extract from normal cerebral tissue; *f*, benzene-alcohol extract from normal dura; *g*, benzene-alcohol extract from a chromophobe adenoma; *h*, benzene-alcohol extract from a meningioma.

TABLE I

Vagus Nerve	Sub-maxillary Ganglion	Normal Dura	Normal Cerebrum	Normal Cerebrum in Formalin	Normal Cerebrum Dried 20 days over Calcium Chloride		Menin-gioma
					Gray	White	
2.86		2.81					
		4.08					
4.2				4.24	4.2	4.2	4.1 f
4.64w	4.7w	4.58w	4.64w	4.64w	4.7 w	4.76w	4.76w
		6.54					
					9.72w	haze	
12.3	12.3	11.22	12.0w	12.0w			
					15.78f	15.36f	

All spacings given in Å
__ = intense line
w = wide, fuzzy band
f = very faint line

of the evaporated extracts—Figures 4*a*, *b*, *c*, and *d* are the acetone extracts from the normal cerebral tissue, normal dura, chromophobe adenoma tissue and a meningioma, respectively. Figures 4*e*, *f*, *g*, and *h* are the extracts of the same tissues using benzene-alcohol following the acetone. Table II gives the complete list of measurements for all of these patterns. It will be noted that there are more lines on the pattern for the adenoma than there are spacings reported. The lines for which there are no spacings given are those from sodium chloride which was in the preserv-

TABLE II

EXTRACTS

Acetone				Benzene-Alcohol			
Menin-gioma	Normal Cerebrum	Normal Dura	Adenoma	Menin-gioma	Normal Cerebrum	Normal Dura	Adenoma
		2.8 m					
	3.48wm					3.36m	
3.74f	3.82m	3.78f					
4.10	4.14	4.08	4.16	4.12	4.09	4.14	4.16
	4.50			4.46		4.52m	
					4.59w		4.56w
4.89w		4.84w	4.77w				
	4.98						
	5.14						
				5.31m			
				5.55		5.63	
	5.85						
	6.3 m			6.28m			
	6.88m			6.74		6.84	
	8.58m						
	13.5			12.70f			
		14.72					
	17.05						

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f = very faint line

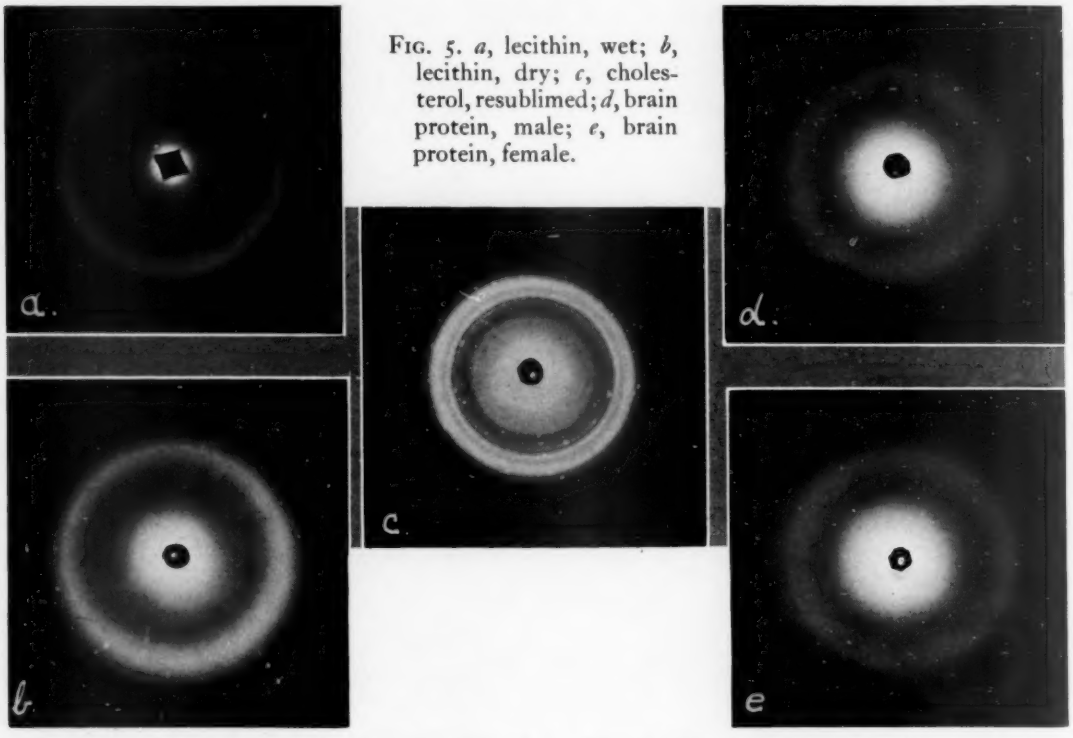

FIG. 5. *a*, lecithin, wet; *b*, lecithin, dry; *c*, cholesterol, resublimed; *d*, brain protein, male; *e*, brain protein, female.

ing fluid. By comparison of these patterns, it can be noted that each specimen gives a pattern or set of patterns which are characteristic of that tissue. The following summary illustrates this point in outline form:

Type of Tissue	*Acetone Extract*	*Benzene-Alcohol Extract*
Cerebrum	Complex pattern	Simple pattern
Dura (note inner ring)	Simple pattern	Complex pattern
Adenoma	Both extracts give similar patterns	
Meningioma	Simple pattern	Complex pattern

The small pieces of material left after extraction were mounted in collodion and examined by the diffraction method. The patterns for these residues are not given separately for they show nothing more than has already been pointed out in whole tissue diagrams. It may be noted, however, that not only these residues and the evaporated extracts, but also the dried tissue to some extent, indicate the presence of a submicroscopic structure in the meningioma, which partakes of the character of both the normal brain tissue and the normal dural tissue.

Since the chemistry of the brain is extremely complicated[12] and as yet very incompletely worked out, it is not possible for us to go far at the present time in identifying the chemical entities responsible for these patterns. Rather the purpose of this research was to find basic information characterizing the various intracranial tumors and nerve structures. Nevertheless, of the pure substances known to be present in the brain, all that could be obtained were investigated. Figure 5 shows lecithin in both its forms, *a* wet and *b* dry. The presence of this substance makes it necessary to proceed with extreme caution, as its pattern varies widely through a whole range of forms depending upon its moisture content. Figure 5*c* is the pattern of resublimed cholesterol. Figures 5*d* and 5*e* are the patterns from male *d*, and female *e* brain proteins. These samples were very kindly supplied to us by Professor Block.[13] With these patterns as standards, we can compare various tissue patterns such as those of the untreated and treated nervous tissues as well as the patterns from the extracts and determine, at least in part,

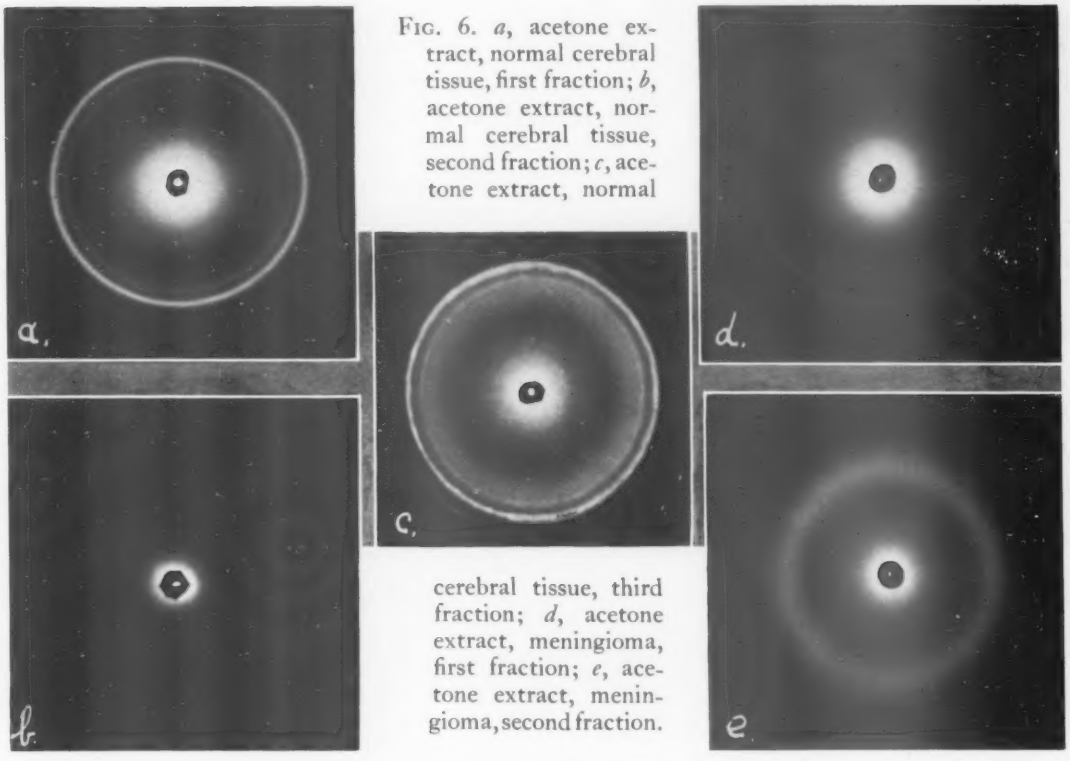

Fig. 6. *a*, acetone extract, normal cerebral tissue, first fraction; *b*, acetone extract, normal cerebral tissue, second fraction; *c*, acetone extract, normal cerebral tissue, third fraction; *d*, acetone extract, meningioma, first fraction; *e*, acetone extract, meningioma, second fraction.

the components of these original samples.

For this purpose of identification, a more complete extraction was run of the meningioma and the normal cerebral material by first grinding it with well washed sand and then extracting in the Soxhlet apparatus for forty-eight hours with acetone. These solutions were fractionally crystallized. There were three easily distinguishable fractions from the normal cerebral extract but only two from the meningioma. Figure 6 *a*, *b*, and *c* gives the patterns for the three normal cerebral fractions while *d* and *e* are the two fractions from the meningioma. Table III gives the spacings for all of these fractions. It will be noted that the second fraction of the normal is mainly cholesterol and the third fraction probably has some lecithin. The meningioma also seems to show some of spacings characteristic of lecithin —14.7 Å, but the percentage is very low as shown by the faintness of the line. By far the largest amount of the second fraction of the meningioma extract would seem to be of a protein material (see Figs. 5*d* and *e*). We wish to mention that when this acetone extraction of forty-eight hours' duration was followed by the usual alcohol-benzene mixture, no residue was left on evaporation of the latter solvent. The explanation offered for this difference between the twenty-four and forty-eight hour extractions is that a clean separation cannot be accomplished by fractional extraction. Hence by running for a longer period of time several components were taken out which were later separated by fractional crystallization whereas the separating was done mainly by regulating the time of

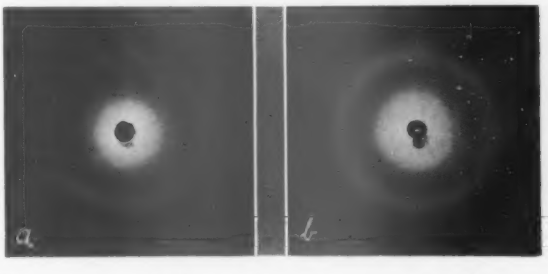

Fig. 7. *a*, cerebral gray matter extracted with acetone; *b*, cerebral white matter extracted with acetone.

extraction with the solvent under the first conditions.

The two patterns (Figs. 7*a* and 7*b*) of gray and white tissue left after extraction with acetone as well as those (Figs. 3*a* and 3*b*) which were dried indicate that there is more than just the protein present since there is a sharpening of the inner ring in the pattern. This along with other indicated changes lends encouragement to continue the search for a satisfactory method of differentiating the various classes and sub-classes of tumors.

Several workers, most recently Schmitt,[14] and others,[15] have supplemented the diffraction work with observations in polarized light. The ordinary polarizing microscope (chemical microscope) or better, the petrographic microscope is adaptable to the study of biological material such as myelin sheath which is known to be birefringent or other biological material which either has optical activity, or in which it can be induced. We will not go into a detailed history of this work, which was started many years ago, since this phase of the subject has been well covered by Schmitt and Bear.[16]

A standard petrographic microscope was used for this work rather than the simple polarizing microscope for it was found that with the material used in this study a great amount of detail could be brought out by the use of the selenite plate. This accessory was discovered about 1813 by Biot, and its use together with the physical basis of its action is fully described in the standard textbooks.[17] By giving a contrast of bright colors the plate makes possible the discovery and determination of very slight double refraction, and the study of very tiny fragments of optically active material.

TABLE III

FRACTIONAL CRYSTALLIZATION OF ACETONE EXTRACTS

Cerebrum				Meningioma			Lecithin		Cholesterol
Total extract	Fractions 1	2	3	Total extract	Fractions 1	2	Wet	Dried over $CaCl_2$	Crystalline
			2.23m					2.24	
			2.48m						
									2.97f
			3.14m				3.16f	3.12	3.18f
3.48wf		3.44f						3.46	3.5 w
3.82m		3.75f	3.74	3.74f					3.80
4.14	4.12	4.12	4.13	4.10	4.15				4.2
4.50	4.58	4.58	4.6		4.58		4.64w	4.66w	4.59
4.98		4.92		4.89w		4.92w			
5.14		5.20							5.06w
									5.28f
5.85w		5.76w							5.94
6.3 m		6.20m							6.30m
6.88f		6.96m							6.98m
8.58m		8.4 m							8.46m
13.50		13.58				14.7m	13.2m	13.1	13.58
17.05		17.05f							17.05

The purified, extracted protein gave only the diffuse band at 4.76Å.

All spacings given in Å
__ = intense line
w = wide, fuzzy band
m = light line
f = very faint line

The introduction of the plate between the crossed nicols causes the field to change (with the stage empty) from darkness to a color which is variously described as "first order red," "sensitive red," "sensitive violet" or simply Biot's original designation "teinte sensible."[18] To us the color is red-violet and the designation "first order red," which is now more or less standard terminology, is used throughout. The color is accurately reproduced in the unoccupied portion of the field in Figure 8*a*. This accessory plate has been of great value to the crystallographer ever since its discovery. In the present investigation crystals which are too tiny for accurate study without the accessory, or which may be largely concealed in inactive material, become clearly visible, and material which is only slightly birefringent takes on the color of the field only when it is at an angle of extinction. In biological material both situations are frequently met in the same specimen.

So far in this study frozen sections have been used entirely, except in special cases where it is better to "tease out" a few fibers, using needles for the coarse work and finally glass hairs. Where sections are studied these are cut as thin as possible by the frozen section method, preferably from fresh tissue, but very little, if any, difference has been demonstrated as yet between fresh tissue and specimens preserved in formalin and saline for a reasonable length of time. To prevent distortion the sections are handled in saline solution in a Petri dish. They are then mounted and covered in the usual manner with a No. 1 cover slip and examined at once. Ordinarily the saline solution makes no difference in the observation, but if the specimen is to be kept for more than an hour or so it is rinsed through several changes of distilled water to prevent possible precipitation of salt crystals as the water escapes. With the specimens of nervous and fibrous tissue so far examined we have not been able to demonstrate that either the freezing or the washing with distilled water caused any disruption or distortion of the structures which become visible in polarized light, although we have investigated this source of error. Specimens which have been heated, or mounted in paraffin or celloidin are entirely unsuitable for study, as are stained specimens in general. The work has been carried on with the close cooperation of Dr. P. F. Morse and the Department of Pathology, and it has been found practical to have both types of investigation made on the same microscopic field by studying the section under the petrographic microscope first and then having the section stained for regular pathological examination. In some cases the gross specimen was divided and one portion mounted in paraffin.

All of the colors shown in the photomicrographs are as seen in the unstained tissue. As might be expected, examination of this untreated tissue by ordinary light does not reveal much detail. With the nicols crossed, myelin and the oriented fibers of the dura stand out sharply and appear brightly lighted in the dark field. If now the selenite plate is introduced, all of these optically active elements show a great deal more detail. Inactive material and fibers having their fiber axes parallel to the optic axis of the system assume the color of the field, as do also those optically active elements which are exactly at an extinction angle. Birefringent material having an axis perpendicular to the axis of the system, and not at an extinction angle, appears in a brightly contrasting blue-green or orange-yellow color. As the stage is rotated these interference colors interchange with each 90 degrees of rotation, with the particle being studied disappearing into the background color exactly as its extinction angle is passing, only to reappear in the next quadrant in the opposite color.

It has been found easy and practical to record the image of the field seen in the microscope by means of color film and a very simple camera. The camera was made from a "Bantam" f 6.3 by removing the lens and fitting an adapter tube, turned out

of an aluminum bar, to the face plate. The adapter tube should fit smoothly over the ocular of the microscope, should permit free rotation without looseness, and must be accurately aligned with the optical axis and perpendicular to the focal plane. Any inexpensive miniature camera may be used, but care should be taken to see that the one chosen has a "time" stop on the shutter. One other accessory is needed for accurate focusing. This is made from a piece of tubing, in this case red fiber, which will fit over the ocular end in the same position as the camera. This tube is slotted at the exact level of the focal plane above the ocular lens and a piece of ground glass inserted and held with adhesive tape. It helps, but is not necessary, to fasten a simple magnifying lens in position above the ground glass and focused upon it. A record photograph is made by focusing the image sharply on this ground glass and interchanging the camera with the focusing tube. More elaborate systems including cameras with lens systems to eliminate the ground glass focusing have been tried and found much less satisfactory.

For the use of color film the exposure must be very accurately determined. We have found the most satisfactory procedure to be the preparation of a strip of test exposures on Eastman Portrait Panchromatic film. The correct exposure time for this film is then multiplied by three for Kodachrome A or by twelve for Dufaycolor. Dufaycolor has an advantage in that it can be processed at once in the laboratory. Kodachrome has other advantages. Examples of both are given.

Figure 8 illustrates the general type of observations which can be made by this method. In addition, exact measurements of refractive index, extinction angles and other crystallographic data can be obtained on very tiny fibers, cell membranes, etc. However, the data of this nature so far obtained must be reserved for later publication.

Sections *a*, *b*, and *c* of Figure 8 show the appearance of a piece of normal dura on the stage of the petrographic microscope. In section *a* two layers of oriented fibers are shown in their original arrangement, crossing each other at an angle of 76°. Sections *b* and *c* show the same field on a single fiber layer and illustrate the color change and the appearance of fiber detail when the stage is moved through an angle of 45°. (May we note in passing that these reproductions are in actual size, and the magnification given is actual magnification. In use these color slides are usually projected onto a 14×17 inch screen for study. In this way a further "empty magnification" of about 13 diameters is gained, which makes the slide much easier to observe, and is in fact the usual procedure with photomicrographic reproductions.)

Sections *d* and *e* are a single fiber from an adult human vagus nerve. The interference colors are illustrated, and in the original a considerable amount of fine detail of the axis cylinder and the myelin sheath are visible. Sections *f*, *g* and *h* are selected from a series of fields. The original specimen consisted of a small piece of dura to which was attached a meningioma about 2 cm. in diameter. The attachment was about 3 mm. in diameter, and the dura was thickened to approximately five times normal around this stem. A suitable slice was cut from the middle of the entire specimen and sectioned. The sections were then examined with the petrographic microscope, a series of fields being taken from the outermost layer of the dura, through the attachment and through the tumor. The field shown in *f* is similar to normal dura but not quite typical; *g* shows an intermediate structure with elements similar to the other two, and *h* is definitely a characteristic structure of a meningioma. The series is offered to illustrate the structural transition from fairly normal dura to meningioma. The field shown in Figure 8*i* is one of particular interest to us, as this small specimen was presented to us as an "unknown" with the hint that "it might be a Cushing's basophile adenoma." Before the petrographic microscope was available

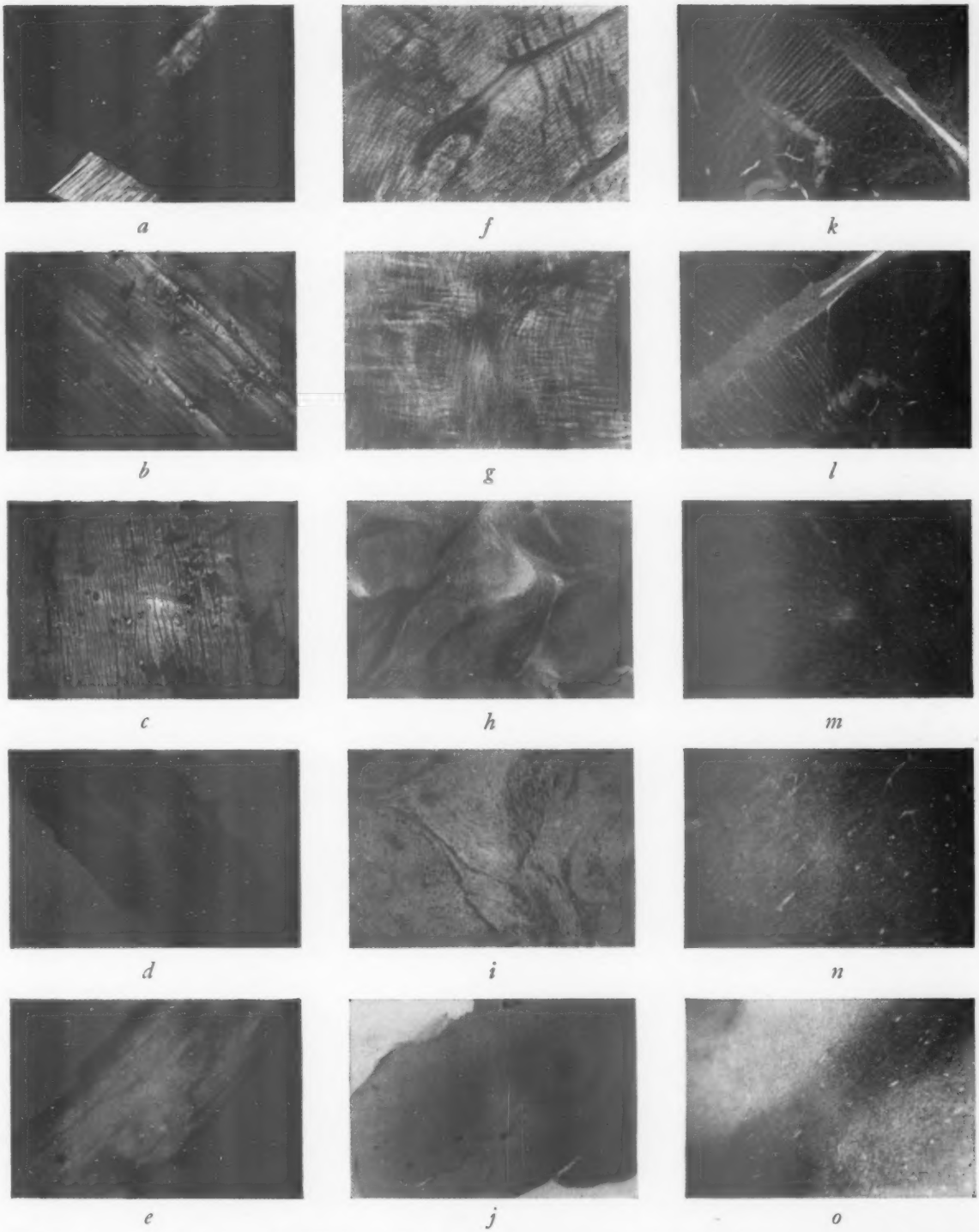

FIG. 8. *a*, normal dura. Two fiber layers in their original arrangement at 76°. Kodachrome ×100; *b*, normal dura, single fiber layer. Kodachrome ×100; *c*, same as *b*, but the stage has been rotated 45°. Note color change and detail of fibers; *d*, normal human vagus nerve, single fiber. Dufay ×450; *e*, same as *d* but rotated 90°; *f*, atypical dura at the point of attachment of a small meningioma. Dufay ×100; *g*, intermediate field between *f* and *h*. Note shortness and random curvature of individual fibers, and color variations. Dufay ×100; *h*, typical field of a meningioma. Dufay ×100; *i*, suprasellar meningioma. Kodachrome ×100; *j*, chromophobe adenoma. Kodachrome ×45; *k*, normal brain stem. Dufay ×45; *l*, same as *k* rotated 90°; *m*, same section as *k* and *l*, showing single nerve cell in olivary nucleus. Dufay ×970; *n*, normal cerebral gray matter. Kodachrome ×100; *o*, normal cerebral white matter. Kodachrome ×100. (Origin of the specimens is acknowledged in the text. All pathological diagnoses by P. F. Morse, M.D.)

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both the extractions and the diffraction patterns had shown the specimen to be a meningioma. The microscope definitely placed it in this class as is shown in the color photograph. The section and the remainder of the specimen were submitted for regular pathological examination and the diagnosis "suprasellar meningioma" was received.

Figure 8*j* is a portion of a proved chromophobe adenoma, and the section shown includes a small portion of the pituitary stalk. Glandular tissue in general gives no interference colors whatever, but it is to be noted that this section shows a tract of bright green points, characteristic of the appearance of nerve fibers. While this evidence is in no way conclusive it is thought that this type of investigation may throw additional light on the debatable question of the existence of nerve fibers in the pituitary stalk. Figure 8*k* is taken through the normal brain stem at a level near the rostral end of the olive. A full and detailed description of the structures found at this level is given in Ranson.[19] In this section and the one following the structures which are at once visible are the median raphe, a portion of the inferior olive, medial lemniscus and a large number of tracts and other structural details. Figure 8*l* is the same field rotated to bring out detail in contrasting color. Section 8*m* is the same slide as *k* and *l* shown under high power. In the upper left quadrant near the intersection of the cross hairs a large single nerve cell of the olivary nucleus is shown. It can be seen that the nucleus, nucleolus, Nissl flakes, chromatin granules and the cell membranes are brought out very clearly by this method.

Figures 8*n* and *o* are normal cerebral tissue taken at random; *n* is normal gray matter, showing on an inactive background a large number of small bright green points where single myelinated fibers have been cut through perpendicular to their axis. These transverse sections are of interest because the entire nerve sheath does not show the same interference color in a given position of the stage. Instead, as the stage is rotated or the focus changed, the spot of interference color is seen to spiral around and up or down the axis cylinder. This indicates that in addition to the types of orientation already studied there is evidently some part of the nerve sheath which has an orientation with a spiral axis of symmetry, which has not yet been investigated. Figure 8*o* is normal cerebral white matter, showing an oriented tract in an inactive background.

This research in no way invades the field of pathology, nor is it intended ever to do so. Rather it is our purpose to investigate by physical means the wide and comparatively unexplored borderland of the ultimate nature of living tissues, of the large molecules and micelles which make up the structures seen in the microscope and upon which so much excellent work is being done at the present time by the ultracentrifuge and by chemical means. In this paper we have tried to give a general survey of the field of study uncovered by correlating the methods of procedure we have described. In subsequent publications we expect to be able to give more conclusive data on a few of the definite points we have mentioned.

SUMMARY

1. Orientation can be noted, in general, in nerve trunks which have a highly specialized directional function.

2. Gray and white matter of the cerebrum give slightly different roentgen-ray diffraction patterns, the difference being shown clearly after drying.

3. Extracted brain tissue gives a pattern very similar to that of neuroproteins.

4. Extracts of some types of meningiomas show characteristics of both normal brain and of dural tissue.

5. Dural tissue is oriented, the degree of orientation varying with the part of the dura being considered.

6. The dura proper and the periosteal layer each have their own well defined

orientation which may be parallel or at angles varying up to 90 degrees.*

To Drs. P. F. Morse and Frederic Schreiber whose help and interest were a great influence in starting and sustaining this research, to Prof. A. J. Derbyshire, Jr., who supplied material, information on neuroanatomy and who with Mr. Robert Emerick assisted us with the actual work, to Dr. Gabriel Steiner who supplied us with material and graciously offered the facilities of his laboratory to cut large numbers of frozen sections, to Dr. Russell H. Morgan who supplied material, and to our large number of friends who have assisted us continuously over a period of more than two years, we extend our grateful thanks.

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* The use of the methods here suggested has been extended to the study of the brains of experimental animals exposed to various dosages of roentgen radiation. A full report of these experiments is now being prepared for publication.

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SOME EFFECTS OF ROENTGEN RAYS ON *SACCHAROMYCES CEREVISIAE**

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ALTHOUGH yeast is one of the easiest laboratory test objects with which to work, only a few radiobiological experiments have been carried out with it and, so far as we know, only Holweck and Lacassagne[2,3,4,6,7] and Wyckoff and Luyet[15] have used it for critical quantitative work.†

While these two pairs of investigators used different species of organisms and somewhat different radiations, their results were generally similar. Holweck and Lacassagne used *Saccharomyces ellipsoideus* and exposed them to ultraviolet (2,800–3,000 Å), soft roentgen rays (8.32 and 1.93 Å) and alpha particles, while Wyckoff and Luyet used *Saccharomyces cerevisiae* and exposed them to ultraviolet (2,536, 2,652, 2,900 and 3,132 Å) soft roentgen rays (1.537 Å) and cathode rays from a Coolidge type cathode-ray tube. Both used quiescent organisms (i.e. from old cultures) and spread them on the surface of agar medium for treatment and culture. The effects observed in both cases were immediate and delayed killing as made evident by differential staining and relative numbers of cells per colony.

The two pieces of work are in agreement in indicating the following: (1) that some cells may be killed outright by the radiations; (2) that others may be injured without being killed; (3) that "S" or skew type (multiple-hit-to-kill) curves are obtained; and (4) that differential quantitative effects are produced by the different qualities of radiation. Both teams of investigators, however, have mentioned that the shifting character of the experimental data tends to cast some doubt on the significance of the findings. Nevertheless, much has been made of the results in developing the so-called "*hit-theory*" of the biological effects of radiation.

The present work was undertaken not so much to improve the methods used previously as to try other procedures which might allow more critical analyses. As will be seen, some important variations were obtained. Since the significance of quantitative work may be judged in part by the experimental procedures and conditions used, considerable detail will be given.

† See references 1, 5, 8, 9, 13 for other qualitative radiobiological experiments with yeasts.

PART I

The yeast technique first employed was developed by Richards[9,10] who has written extensively on the growth properties of this organism and who spent a week in this laboratory carrying out the first irradiation experiments. We take pleasure in expressing our appreciation and indebtedness to Dr. Richards for his interest, cooperation and kind assistance.

Procedure

The procedure used was to expose actively growing cultures of the organisms to varying amounts of radiation and to determine the relative population densities at varying times following irradiation. For this it was necessary to make numerous determinations and do so in a way that would not disturb the growth activities of the cultures. This was made possible by using a photo-cell instrument developed previously by Richards and Jahn.[12]

Yeast, as do many unicellular organisms, manifests a rate of growth which is exponential with time when the growing conditions are optimum. As waste products accumulate and nutritive materials decrease, the rate drops off. The experiments to be described here were carried out in such a way that treatment was ad-

* Acknowledgment is made to the United States Works Progress Administration of New York City for assistance rendered under Project Number 125.

ministered early in the logarithmic phase of growth and determinations of the relative number of organisms present were made during the remainder of this phase and during part of the phase of decreasing growth rate. While we actually measured population densities at various times and thus the rate of growth, the data can be used in a unique way to indicate the relative number of organisms killed by the radiation and how this varies as a function of dose.

The yeast used was a strain of *Saccharomyces cerevisiae* obtained originally by Richards a few years ago from a single cell isolation. It has been maintained at 26°C. on either liquid or solid media. The liquid medium (Williams[14] and Richards[10]) consisted of 20 grams of table sugar (sucrose), 3 grams of ammonium sulphate, 2 grams of potassium di-hydrogen phosphate, 1.5 grams asparagin, 0.25 gram of calcium chloride, 0.25 gram of magnesium sulphate in 1 liter of distilled water. For solid media 23 grams of Bacto-Nutrient Agar was added to the above. To obtain material for the experiments, organisms were transferred from an agar slant to liquid medium. This was done by placing a straight platinum wire in the center of the slant colony, moving it back and forth over a space of about 1/8 inch and transferring at once to a tube containing 13 cc. of liquid medium where the wire was washed free of the inoculum by moving through the medium. The inoculated material was then allowed to incubate for three days after which 3 cc. of uniform suspension was diluted with 27 cc. of fresh liquid medium. Thus 1 cc. of this culture represents 0.1 cc. of three day old culture. This was the material used for experimentation and will be referred to simply as the *test material.*

One cubic centimeter of test material was transferred by means of sterile pipettes to each of twelve celluloid containers. These were circular, 2.46 cm. in diameter, 1.2 cm. deep and fitted with covers. The thickness of the celluloid of the containers and the covers was 0.3 mm. Two containers with media were placed in a sterile petri dish and kept as controls. The other ten were placed on a thin (0.1 mm.) celluloid tray and arranged under the roentgen tube for exposure. The reason for using celluloid in these two places was to avoid as much as possible complications arising from scattered radiation.

Treatment

Exposures were carried out using a roentgen machine under the following conditions: 200 kv., 30 ma., 33.6 cm. distance and no filter except the heavy glass of the roentgen tube (0.6 cm.). The intensity of the radiation at the point of treatment (measured in air) was 291 roentgens per minute. The output was kept constant during treatment by means of a galvanometer which was attached to an ionization chamber that remained in a fixed position in a part of the roentgen-ray beam not being used for treatment purposes. Two celluloid containers were removed after receiving each of the following exposures: 0, 8, 16, 32, 64, and 128 minutes.

After treatment the irradiated material together with the non-irradiated controls were transferred to culture tubes (Pyrex test tubes 1.5 cm. in diameter and 15 cm. in length) and further diluted with liquid medium. This was done with a sterile pipette and rubber bulb, one for each individual sample. The test material was drawn up from the celluloid containers and squirted into culture tubes containing 13 cc. of liquid medium. Some of the medium was drawn back into the pipette in each case and used to wash the remaining yeast cells from the containers and pipettes. Thus, the final culture material consisted of 0.1 cc. of three day old culture in 13.9 cc. of fresh medium and 1 cc. of the test material in 13 cc. of fresh medium. These quantities were used to facilitate experimental manipulations and have no other significance.

Measurement of Effect

As mentioned above the population density at various times was determined photometrically by measuring the amount of light transmitted through the medium containing organisms. The apparatus used consisted of four essential parts: (1) a fixed source of light with canalized beam; (2) a block to hold the culture tube properly in the beam; (3) a photoelectric cell; and (4) a milliammeter to measure the current generated by the light absorbed in the cell.

Before setting up the cultures, culture tubes were selected which gave the same milliampere reading on the instrument when placed in the holder with the Pyrex label always towards the operator. This tended to minimize peculiarities in readings due to irregular optical properties of the culture tube glass.

As is evident at the outset a constant light source is essential if consistent readings are to be had. Since electric current from an ordinary 110 volt alternating current outlet was used to

light the bulb and since a certain amount of line-variation seems inevitably to occur despite the use of a ballast tube, it was necessary to take certain precautions to insure reliable readings. To do this a tube of sterile medium was placed in the supporting block at the beginning and a reading taken. This was found to be near 350 microamperes. This figure was then adopted as a standard reference value and the instrument made to give this reading consistently both before and after every experimental reading. If any discrepancy was found the experimental value was discarded, the reference value of 350 again obtained by moving the support block (which is mounted on a rack and pinion carriage) nearer to or farther away from the light source and then a correct experimental value obtained.

Results

Readings were taken twice daily, usually about 9 A.M. and 5 P.M. for about a week following irradiation, the specific time when the readings were made being recorded in each case. Results obtained would have been easier to handle if the readings had been taken routinely at the same time each day. However, since the work at this point was largely exploratory in nature the importance of such procedure was not realized until after a number of experiments had been completed. Thus in order to avoid the necessity of presenting a complicated table of values and to allow the reproducibility of the experiments to be judged, all values have been plotted (Fig. 1).

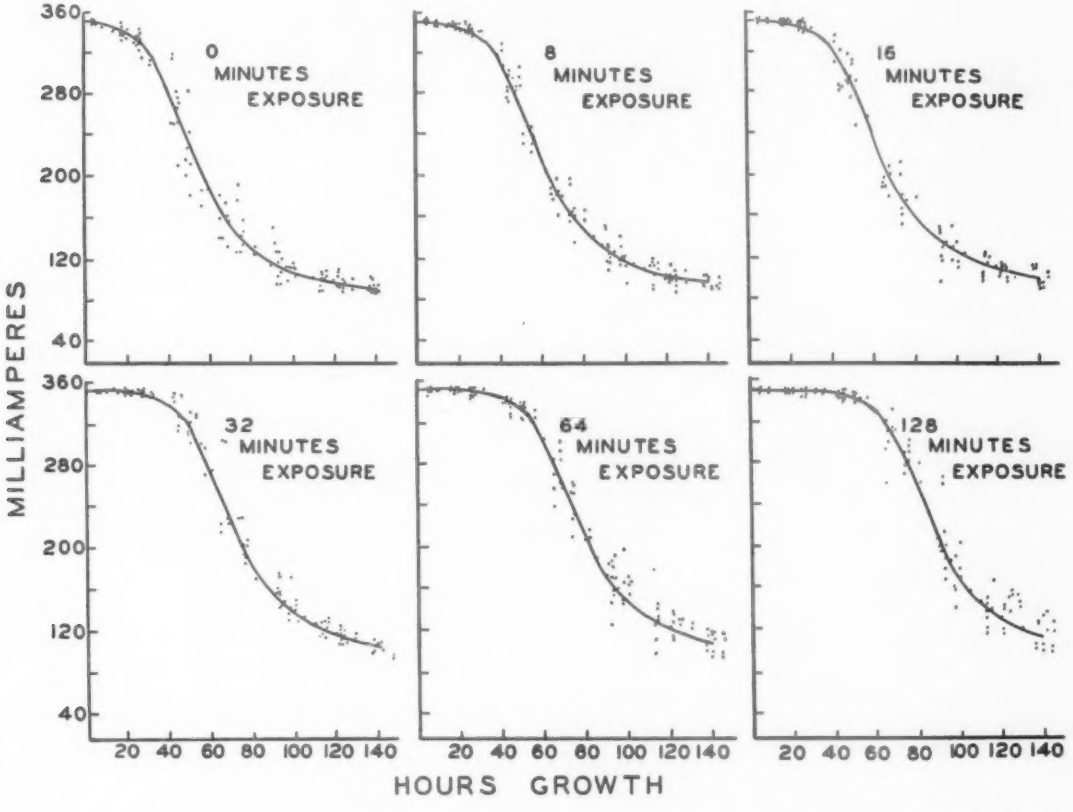

Fig. 1. Yeast growth curves after different exposures to roentgen rays and obtained with the photo-cell instrument. The abscissae show hours' growth following irradiation and the ordinates milliamperes read on the instrument. The curves have been drawn down to the level of 160 ma. in such a way that the horizontal separation between them is constant. Below this point they have been drawn to fit the experimental points in each case.

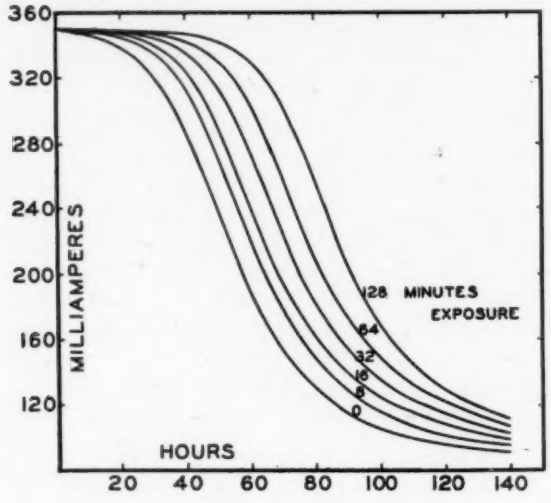

FIG. 2. A reproduction of the curves of Figure 1 in the same graph.

In Figure 1 the abscissae indicate hours growth following irradiation and the ordinates milliampere readings taken from the photo-cell instrument. Since the milliampere values become smaller as the number of organisms increases (growth), the downward trend of the curves indicates greater population density.

In an attempt to analyze the results a number of things were done. First of all the best possible smooth curves were drawn free hand through the points. From this alone it became evident that the curves were displaced to the right in accordance with the amount of radiation given and that they bore a strong resemblance to each other (better seen in Fig. 2).

In order to get a more definite idea of this resemblance, abscissae readings for corresponding ordinates were taken from all the curves. Examination of these disclosed that the abscissa distance from any one curve to another was practically the same at all levels. This interesting observation, if true, indicates that the growth, once manifest after treatment, continues at the same rate irrespective of the amount of radiation given.

To investigate this further, trial and error adjustments of the curves were made to see whether a set with constant horizontal differences could be made to fit the experimental points as well as any that could be drawn. The curves as drawn in Figures 1 and 2 bear such relationships to each other down to the level of 160. Below this, those for the more heavily irradiated material tend to become parallel with the abscissae somewhat more quickly. Accordingly the distances between the curves are slightly greater in this region. In any case, however, the deviations are small as may be seen in Figure 2. Since a constant difference is well manifest throughout the greater part of the curves and especially in the more significant region, it seems safe to say that for the most part the rate of growth of irradiated and non-irradiated organisms is the same—once it becomes detectable—irrespective of the amount of radiation administered. The meaning of this will become more evident below.

The degree of separation between the curves of Figure 2 may be taken as a biological measure of irradiation effect. In accord with this, readings were made from the curves in the region where the slopes

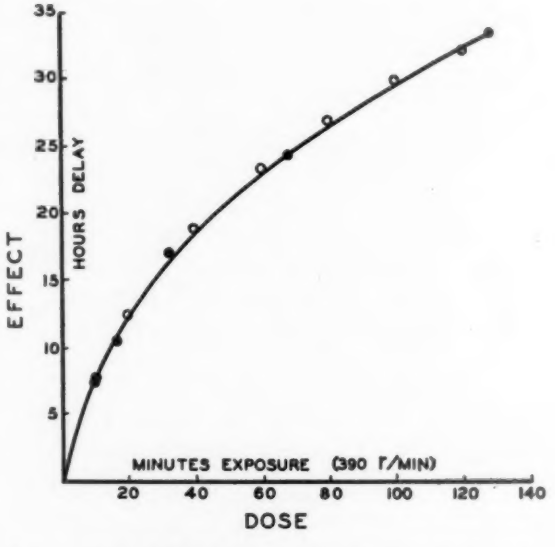

FIG. 3. Dose-effect curve showing hours' delay in the onset of growth as a function of minutes' exposure to roentgen rays. The closed circles represent experimental values whereas the open ones represent calculated ones (see text).

were the same and the differences calculated, taking the reading for the controls as zero. The data thus obtained are plotted in Figure 3 (closed circles). Figure 3, therefore, is a curve showing how the irradiation effect in terms of hours delay varies as a function of dose—a form of dose-effect curve.

As will be seen, the experimental points may be fitted with a smooth curve which rises rapidly at first and then more and more slowly. Before discussing this, however, let us return to Figure 2 and also present certain other tests.

It has been pointed out that the growth curves (Fig. 2) are displaced to the right in accord with the amount of radiation administered and that they are a constant distance apart over their significant range. Since we were measuring growth, the displacement indicates a delay in the onset of the growth process as detected with the photo-cell instrument. Consideration of the delay process caused us to undertake other experiments which have helped considerably in understanding the meaning of the dose-effect curve.

PART II

It became clear that delay in the onset of growth as indicated by the photo-cell measurements must have been caused in one of two ways by the radiation: (1) either by production of a physiological block thus causing the organisms to remain quiescent for varying periods of time following treatment, or (2) by certain organisms being killed outright by the radiation and others being unaffected.

Superficially, the first explanation seemed most satisfactory in view of the fact that organisms of this type sometimes tend to form inactive spores when unfavorable growing conditions are encountered. However, it was difficult to visualize how they could be quiescent at one moment and then at the next suddenly manifest the normal rate of growth, which is what appeared at first to be taking place.

By going back over the experimental conditions certain things were found which caused this explanation to seem less probable. It will be remembered that 350 milliamperes was the reading on the photo-cell instrument when a tube of sterile medium was used. Furthermore, it will be seen (Fig. 1) that a reading of 350 was also obtained when the tubes were freshly inoculated with test material and that this was true whether the material was irradiated or not. Thus, it was not possible to detect with the methods used whether organisms had been killed outright by the radiation or simply rendered quiescent for a period of time.

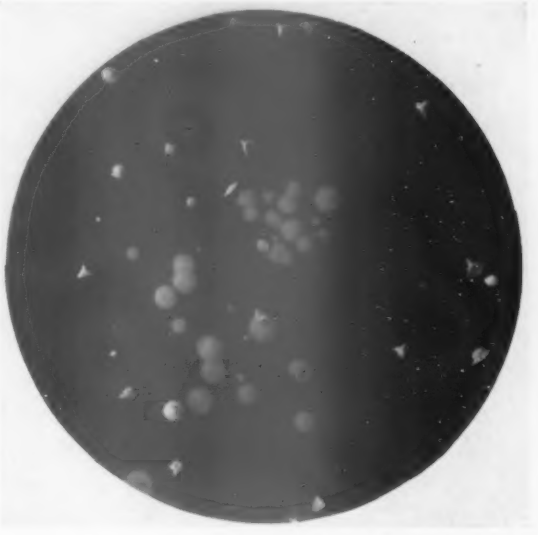

Fig. 4. Photograph showing the two characteristic forms of colony growth on agar plates (*Saccharomyces cerevisiae*, ×5).

It was therefore decided to culture the organisms, both controls and irradiated, on agar plates in such a way that the resulting colonies could be observed. This was done to determine two things: (1) whether any organisms were killed outright by the irradiation; and (2) whether the colonies resulting from irradiated material developed any more slowly or showed any loss of vigor when compared with those resulting from non-irradiated material.

Procedure

Solid medium was prepared as described above and allowed to cool almost to the point

of gelation (approximately 42° C. which is about 3–4 degrees above the gelation temperature). One cubic centimeter of the test material was transferred to the center of a Petri dish by means of a sterile pipette. About 10 cc. of sterile agar medium (as prepared above) was poured directly over the culture and the plate rotated gently to insure a uniform distribution of the organisms throughout the medium. The medium was then allowed to solidify before being inverted and put away in the incubator at 26° C. After four days the colonies of organisms appear on the plates as shown in Figure 4. While the photograph shows a magnification of several diameters (4–5) the colonies may easily be seen and counted with the unaided eye.

The dilutions were such in this procedure that the colonies which arose in the culture dishes came from individual yeast organisms or colonies consisting of a few cells (see Figs. 8 and 10, Part IV). The colonies which developed were of two kinds as is characteristic of this form, a diffused type with smooth outline and an irregular type with a varying number of fantastic projections. Pure cultures of either type give rise to both smooth and irregular shaped colonies, both of which can clearly be seen in the photograph (Fig. 4).

The response of the organisms to irradiation when the plating procedure was used is shown in Figure 5. Going from left to right the test samples received respectively 0, 16, 32, 64 and 128 minutes' exposure to the radiation described above. The top row of plates was inoculated with one-tenth as many organisms as in the bottom row.

It will be seen first that there are consistently more colonies appearing in the dishes in the bottom row which is in accord with the dilutions made. A direct count of all the colonies present in corresponding pairs of plates shows the number in the top row to be approximately one-tenth that in the bottom row. Second, it will be seen, passing from left to right, that there are fewer and fewer colonies, the number thus dropping off in accord with the amount of radiation administered. Third, the size of the colonies appears not to be affected in any significant way by the irradiation, those in the heavily irradiated samples being fully as large as the largest of those in the non-irradiated. It will be seen that the colonies in the more concentrated samples are generally smaller—a condition well known to be associated with crowding. This, however, does not interfere with statement number three. These observations therefore yield answers to the points in question.

Finding fewer and fewer colonies in the samples receiving increasing amounts of exposure showed clearly that the delay indicated by the curves above is not due to a block in growth activity but to the outright killing of some of the cells. Furthermore, finding that the size of the colonies was in no way made smaller indicates that the vitality of the living forms was not appreciably, if any, diminished or impaired by the irradiation. This manifestation of unimpaired vitality is in accord with the photo-cell observations above, indicating that the rate of growth of the organisms remains the same irrespective of the amount of radiation applied.

Turning again to the dose-effect curve (Fig. 3), it will be recalled that this is a plot of values representing the horizontal distances between the curve for control material and those for the irradiated (Fig. 2). Since it has just been indicated that these distances result from a decrease in the number of viable organisms in the irradiated samples, it becomes clear that the dose-effect curve is actually a type of mortality curve—one showing in some way the relative number of organisms killed as a function of the amount of radiation administered.

The dose-effect curve may now be analyzed in the light of this and other conclusions thus far formulated.

Two significant characteristics of the curve are apparent at the outset. (1) It rises abruptly at the beginning and (2) its slope becomes less and less. It is therefore in striking contrast to the "S" or skew type killing curve obtained by the previous investigators. The abrupt rise indicates that no appreciable threshold dose is required before some manifestation of effect is apparent, and the decrease in slope that fewer and fewer organisms are killed per unit quantity of radiation as the dose is increased. In regard to the latter, it may be said that since the total number of organisms killed increases continually with dose, the dropping off of killing action may be correlated with the decrease in number of viable organisms present. Thus, it would appear that as the concentration of living forms becomes diminished, the number of organisms killed per unit quantity of radiation administered also is diminished. Considering then the fact that radiant energy is absorbed as discrete units or quanta, the loss in effectiveness of the radiation (per unit quantity) may

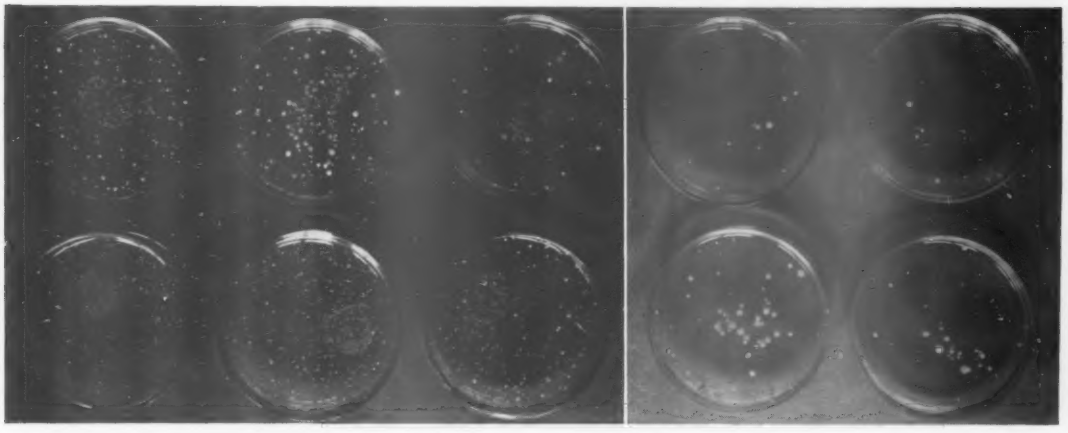

Fig. 5. Agar plate cultures of *Saccharomyces cerevisiae* showing different dilutions and the growth following varying exposures to radiation. The plates in the upper row had an original concentration one-tenth that of the ones in the lower row. Going from left to right the plates in both rows received respectively 0, 8, 16, 32, 64 and 128 minutes' exposure to roentgen rays (390 r/min.). Three significant things may be noted: (1) that the colonies in the more densely populated dishes are smaller whether receiving radiation or not; (2) that the colonies appear to be unaffected by the irradiation and (3) that the number of colonies present becomes less as the dosage of radiation administered is increased.

be attributed to the decrease in probability of encounters of energy quanta with photosensitive receptors in the organisms.

The curve (Fig. 3) was tested to determine whether it is of the exponential type, the type which would be expected if the action observed were due to the probable encounters of energy quanta with photosensitive parts in remaining viable organisms. The expression $e^{ky}=ax+b$ was used for this purpose. The open circle points (Fig. 3) were thus obtained when $k=0.0678$, $a=0.065$ and $b=1$. The points will be seen to lie on or very close to the experimental curve.

It is to be noted, however, that any slight shift in the position of a curve in Figure 1 (which might easily occur if more experiments were carried out) would cause a change in the curve (Fig. 3). Because of this, it seemed advisable to carry out a different kind of experiment in order that further information on the meaning of the results here might be obtained.

PART III

In order to obtain a more direct measure of the killing rate produced by the irradiation, a survival curve was derived by making plate counts of colonies arising from samples given different amounts of radiation. More precisely, counts were made of colonies found in cultures treated and prepared as shown in the upper part of Figure 5. Seven such counts have been made on different preparations of material and the results are shown in Table 1. Since com-

Table I

YEAST PLATE COUNT EXPERIMENTS

Minutes Exposed	0	8	16	32	64	128
Experiment No.						
1	327	271	248	232	185	110
2	239	201	187	140	122	88
3	163	150	139	121	103	66
4	216	198	148	136	104	—
5	236	203	172	148	109	88
6	430	294	240	210	171	98
7	204	165	156	132	97	55
			Percentage			
1	100	83	76	71	57	34
2	100	84	78	59	51	37
3	100	92	85	74	63	42
4	100	92	69	63	48	—
5	100	86	73	63	46	37
6	100	68	56	49	40	23
7	100	81	76	65	48	27
Av.	100	84	73	63	50	33
σ	—	4.8	8.4	7.6	7.0	6.6

pletely new material was used in each preparation, it was possible to have only approximately the same concentration of organisms at the beginning in each case. This, in the main, accounts for the differences in cell number of the controls and corresponding experimental samples as shown in the table (upper part). This, however, does not interfere with the investigation for the percentages run generally the same as may be seen in the lower part of the

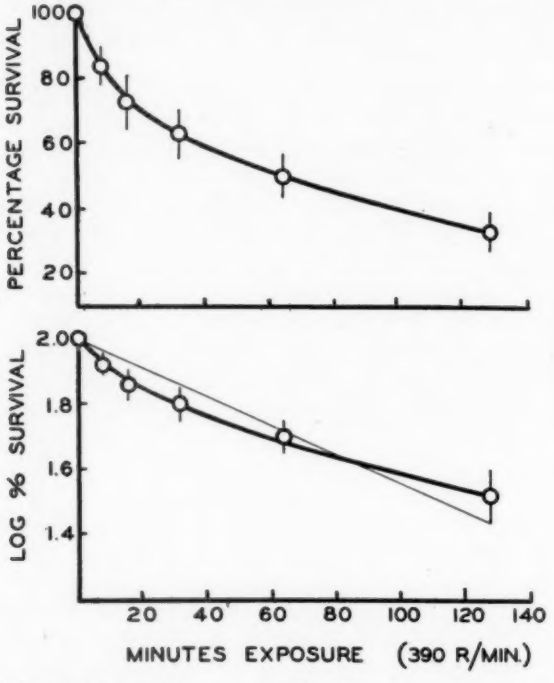

FIG. 6. Dose-effect curves showing percentage surviving (ordinates) as a function of roentgen-ray dosage (abscissae). The upper part shows the percentage surviving plotted in the usual way, whereas the lower part shows it plotted as logarithms.

table. Averaged percentage values, together with their standard deviations (σ) have been calculated and plotted in Figure 6 (upper part).

Examination of the curve indicates, as before, that no significant threshold dose of radiation is required before an effect begins to be manifest and also that the curve is of the die-away type. In the lower part of the figure, logarithms of the averaged values have been plotted. It will be seen in this case that the best curve through the points tends to dip, but that a straight line may be drawn which falls almost within the limits of the standard deviations. The regularity of the points with respect to each other, however, is such that doubt is cast on the possibility that the curve is exponential. This, nevertheless, may be said: the deviation from the strictly exponential form is in a direction to avoid all confusion on the question of a threshold effect. Certainly there is not the slightest possibility that the curve is of the skew type.

PART IV

At this point an odd question enters in. It will be remembered, and it will become very apparent below, that the yeast forms were irradiated not only as single cells but also as groups or clusters of cells. Thus, since presumably every mature cell is capable of independent existence, it is difficult to understand how single radiation quanta can, as indicated above, produce killing in the multicellular forms unless death in a single cell causes death in all the cells of a colony.

To investigate this, certain microscopical examinations were carried out.

The first of these was a vital staining experiment with methylene blue. When this stain is applied properly, the living cells can usually be distinguished from the non-living since only the non-living ones tend to take up the dye. Briefly, it was found that exposure to large doses of radiation did not change the appearance of the organisms appreciably so far as their ability to take up stain was concerned. Occasional stained cells were observed, but they occurred equally as often among the treated and non-treated samples. Following exposure, those colonies which fail to develop do not take up the blue stain as do those that have been killed by boiling or fixation. In general, they show no change whatsoever for several days while the developing forms undergo extensive proliferation. The methylene blue technique, therefore, fails to indicate that the yeast cells are killed

individually by the radiation and leads to the presumption not only that the colonies respond as units but that their death does not occur for some time after they have lost the power of proliferation. Actual proof of this, however, has not been obtained as yet.

Parenthetically, we may describe here the photograph (Fig. 7) which shows something of the rate of proliferation in the yeast cells under normal conditions. While this point does not have a direct bearing on the question being discussed, it is one that invariably comes to mind when pondering the mechanism of action here. A fresh plate culture was prepared about 9 o'clock on the day photographs were to be made. A single cell was found and photographed as shown at the beginning of the series. At 11:00 o'clock two cells were observed as shown. Considering now the daughter cell, it was found to have a beginning bud at 11:20. If the bud be followed in the photographic series, it will be found to have matured and produced a similar bud by 2:05—slightly more than two hours. Several instances of this kind may be found in the series and the division interval seems to range from a few minutes less than two hours to a few minutes more than this figure for the conditions used. As maintained under the microscope in an enclosed hanging drop of solidified agar, the culture was kept at a temperature 3–4 degrees below the usual culture temperature of 30° C. Accordingly, the time for division was undoubtedly somewhat less than two hours for the experimental conditions. At best, this figure can be only an approximation, for different cell groups may differ significantly in their proliferative rates, but it gives some idea of the division time.

Other microscopical examinations were carried out to compare the appearance of the irradiated and non-irradiated materials. This, in part, was a further attempt to determine whether any damage occurred in organisms surviving large doses of radiation. Figure 8 shows a series of photographs of both non-irradiated and irradiated forms, the latter having been exposed to 25,000 roentgens (64 min., 390 r/min.). The photographs were made twenty-four hours after the treatment and plating procedure had been completed. Figure 9, likewise, shows similar materials 120 hours after treatment and culture. The specimens shown were selected to show that colonies of all sizes are present in both irradiated and control samples. Moreover, it will be seen that there is no significant difference in the appearance of the two kinds of material. Subcultures prepared of both irradiated and non-irradiated materials taken from the large colonies grow identically as nearly as can be ascertained. The findings, therefore, bear out the observations above that colonies which survive the radiation treatment appear to behave as though they had received no treatment at all.

While colonies of all sizes were found in both treated and untreated samples, the photographs (Figs. 8 and 9) show nothing of the frequency of occurrence of colonies

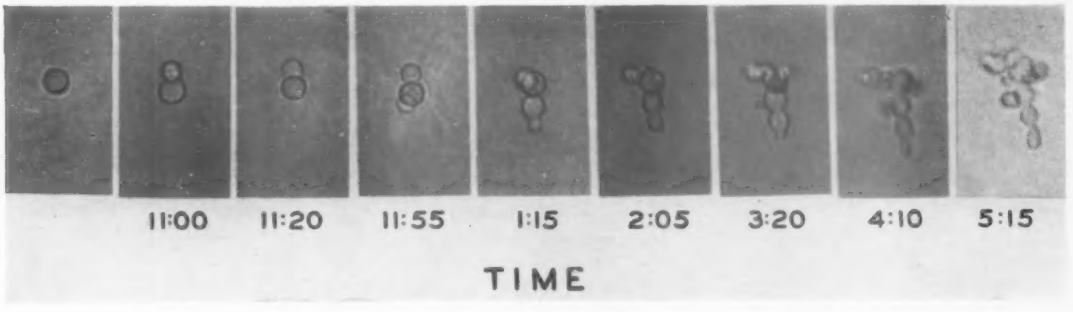

Fig. 7. Photographic series showing the growth of a yeast colony (see text).

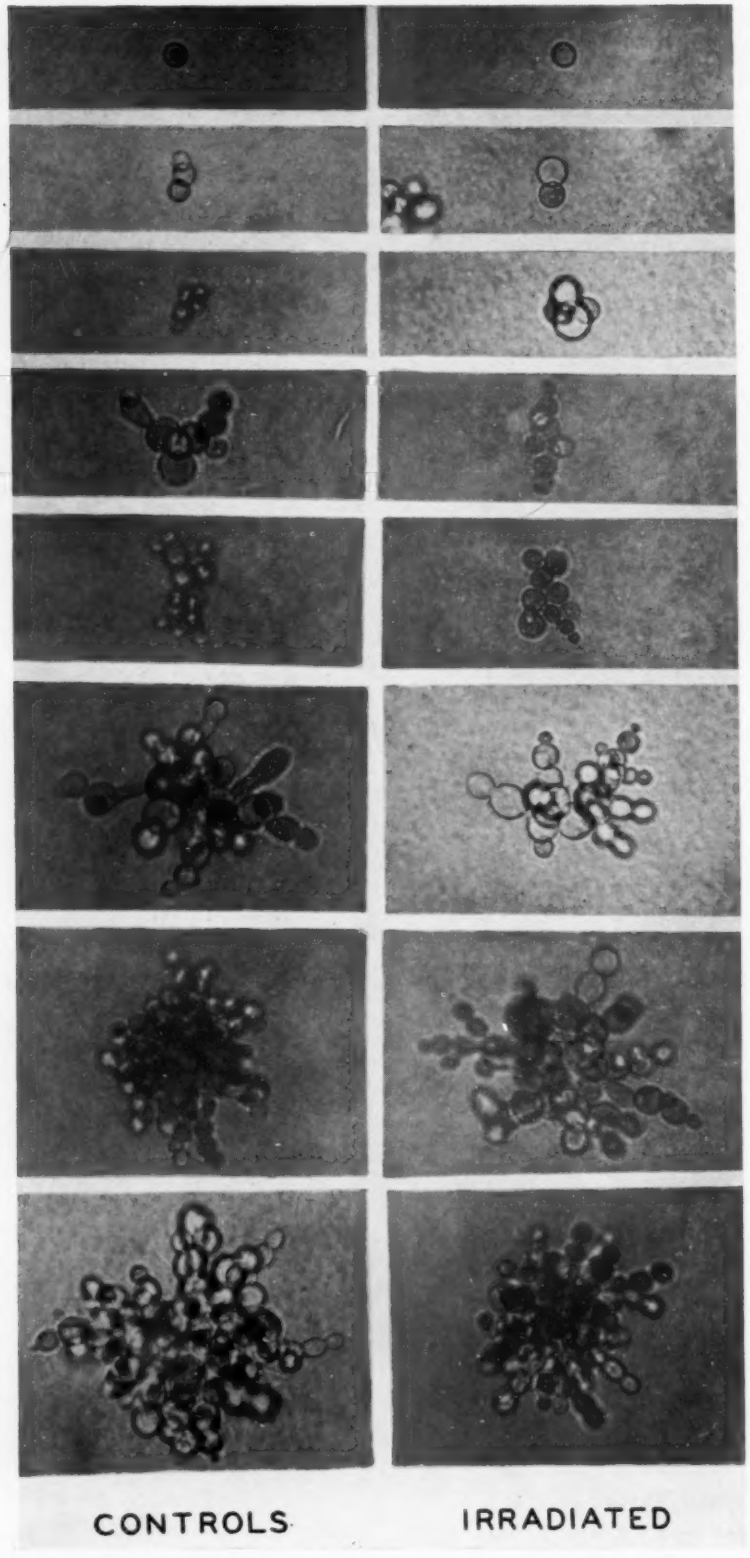

FIG. 8. Photographic series showing the lack of visible irradiation effect on colonies of different sizes. The photographs were taken twenty-four hours after treatment and seeding into the agar plates. (×400).

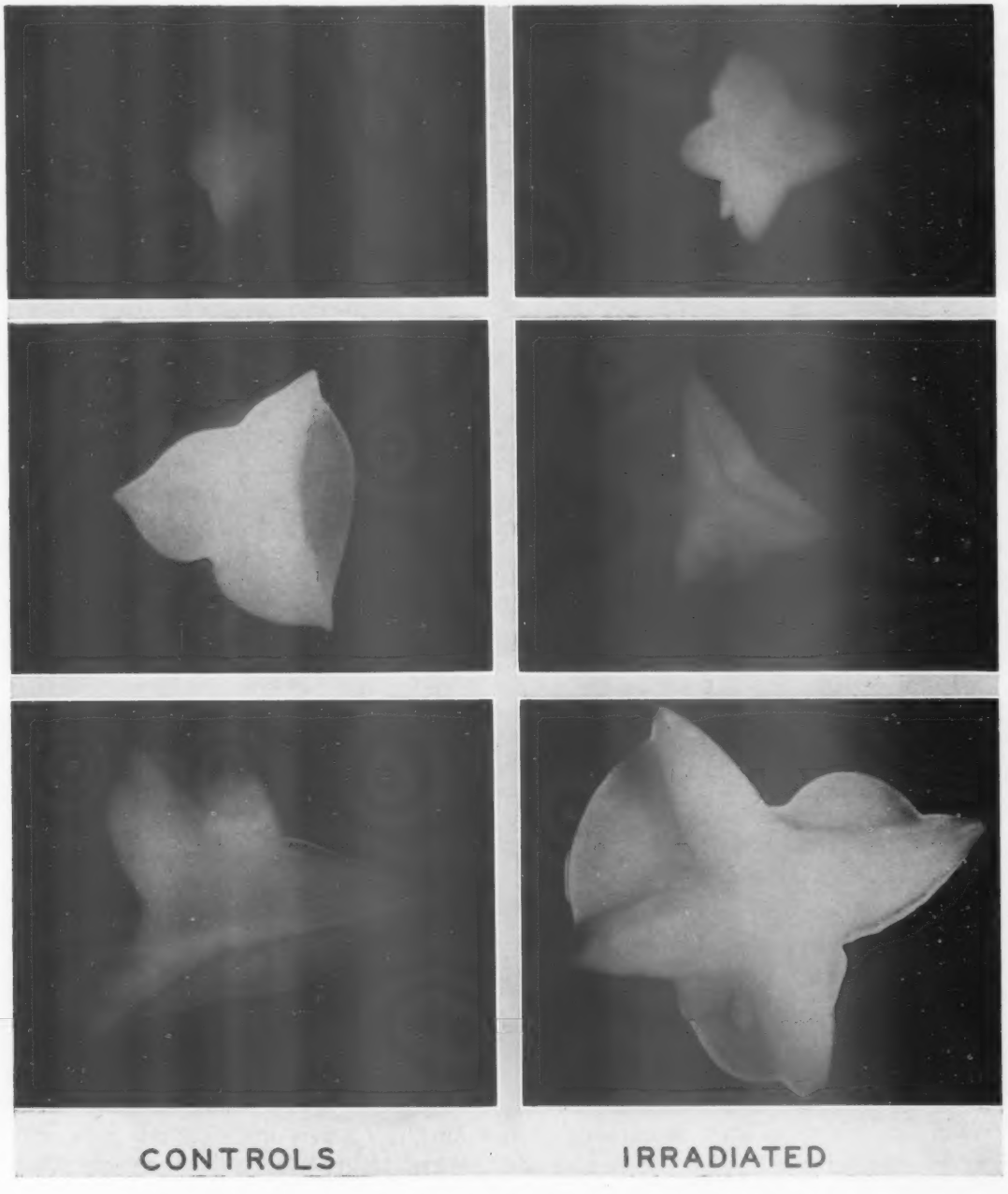

Fig. 9. Same as Figure 8, 120 hours after treatment and seeding (×15).

of different sizes. To obtain an idea of this, counts were made of the number of cells per colony in a large number of colonies selected at random. This was done for irradiated and non-irradiated material and for material of different ages. One to two hundred colonies were counted for each condition considered in five different sets of experiments. The averaged results are shown in Figure 10. The classes used (2, 3, 4–5, 6–8, 9–12, 13–17, 18–25, 26–40 and 41- cells) were selected arbitrarily to facilitate counting since in the large colonies it was sometimes difficult to be certain of the precise number of cells and also to make the results more manageable. A good many

single cells (perhaps 5–10 per cent) were present but since it was easy to confuse these with artefacts in the medium (small bubbles), they were simply omitted from the consideration.

Examining Figure 10, it will be seen that at the time of culturing, no colonies had more than twenty-five cells and that most of them had less than eight; this was true both for irradiated and non-irradiated materials. Within four hours, however, a definite shift had occurred in both, this perhaps being a little greater for the controls. By the end of twenty-four hours more than 90 per cent of the controls had become colonies of more than forty cells whereas only about 40 to 45 per cent of the irradiated colonies had reached this stage, those not reaching it being distributed among all the lower classes. By the end of forty-eight hours this picture had not changed appreciably so far as this classification was concerned.

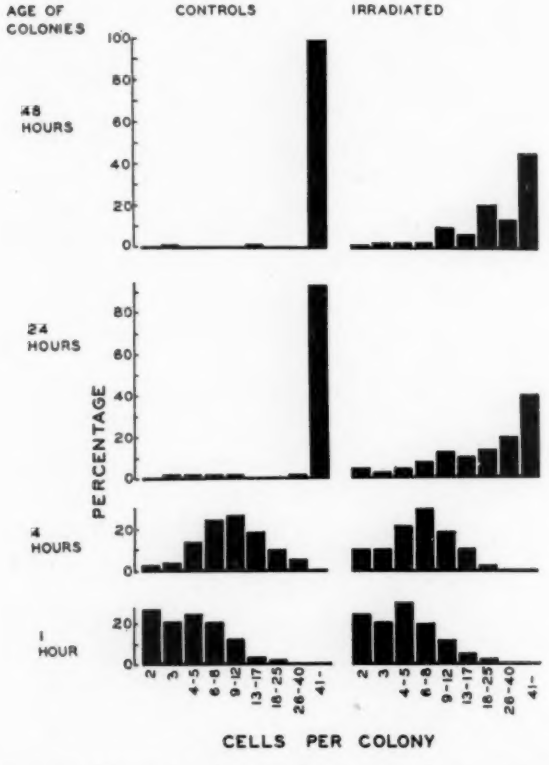

FIG. 10. Chart showing the frequency of colony size with respect to cell number for irradiated and non-irradiated materials at different times after treatment and seeding into the agar plates.

Close examination of the results shows that about 45 per cent of the irradiated colonies reach the forty-cell stage. This value becomes especially interesting when it is noted in Figure 6 that the percentage of colonies developing to the point of visability (with the unaided eye) is about fifty for samples receiving the same treatment of 25,000 r and the same handling. The two values, therefore, are significantly close together and indicate that if irradiation damage is produced in the colonies by the irradiation, they seldom, if ever, go beyond the forty-cell stage. It is clear from these findings, therefore, that some but only a small amount of proliferation follows the effective action of irradiation on the cells.

DISCUSSION

The results presented here differ in certain respects from those of Holweck and Lacassagne and of Wyckoff and Luyet: (1) whereas they observed immediate killing, we observed several cell divisions among those cells (or colonies) which died as a result of exposure to radiation; (2) whereas they observed partial injury, we observed only complete killing; and (3) whereas their dose-effect curves, for all radiations used, showed a significant threshold dose, ours indicated none.

The first two discrepancies, however, seem more apparent than real when the different criteria of effect are taken into account. Holweck and Lacassagne divided the organisms affected by the radiation into three classes: one in which no cell division occurred, "immediate death";* one in which a single division occurred, "deferred death"; and one in which more than a single division occurred. Wykoff and Luyet likewise used these criteria but in addition classified the colonies formed as to number of cells up to the eight-cell stage. We, on the other hand, allowed the cells that would

* Single cells (not colonies) being inferred for the beginning of the experiment.

do so to form colonies and by following closely what happened found that colonies of more than eight cells may be reached before death from irradiation occurs. Thus, it would seem that the previous investigators might have observed a greater percentage of killing in the total population if a longer period of development had been allowed. Holweck and Lacassagne, in fact, state that the proportion of the three classes of abnormalities changed with time.

Because we have found that irradiated colonies which survive to the forty-cell stage grow normally and manifest no detectable injury, we are able to emphasize the all-or-none action of irradiation on yeast and that the reason why the previous workers observe partial injury was probably because the irradiation effect was not fully manifest when measured.

The third point, difference in shape of survival curves, is more difficult to deal with. In view of the fact that we are here working with an affecting agent consisting of discrete quanta, a test object made up of individual cells (or colonies) and a response that is complete killing, the shape of the survival curves, as mentioned above, may be taken to indicate certain basic characteristics of the reaction in progress. Thus the difference between our curves and those of the previous investigators is a matter of importance.

Two factors may be mentioned in this connection: (1) species of organism used, and (2) wave length of radiation used.

It seems unlikely, however, that the differences observed can be attributed to species of organism used for although Holweck and Lacassagne used *S. ellipsoideus*, Wyckoff and Luyet used *S. cerevisiae* as did we. By default, therefore, the matter of wave length dependence comes to the fore. Interpreted on this basis, the difference between the non-sigmoid curves obtained by us and the sigmoid ones obtained previously must be taken to mean that somewhere along the wave length scale between the quality of radiation used by us and that used by the previous workers, the reaction changes from the one-hit-to-kill type to that of the multiple-hit-to-kill. Although this seems the most likely interpretation at present, we are unwilling to accept it. This unwillingness is due largely to questions arising in connection with the colonial character of the organisms at the time of treatment. The results in Part IV above indicate that death in a single cell causes death in the colony of which it may be a part. While this finding is consistent with the shape of the curves obtained, it is not consistent with what has been believed in connection with the biology of yeasts. To investigate the shape of the survival curve further, it seemed advisable to use a non-colony-forming species and thus eliminate the uncertainties associated with multicellular test objects. This avoids the interesting question of the influence of a damaged cell of a colony on the other cells of that colony, but seems to be the best procedure at present.

SUMMARY

1. Experiments have been carried out to investigate the action of roentgen rays on *Saccharomyces cerevisiae*. For the first work, the growth of samples receiving varying amounts of radiation was determined by measuring the turbidity of the suspensions with a photo-cell instrument. A family of curves was obtained which indicated that the growth processes were delayed in some way by the irradiation but not impaired by it.

2. The delay, plotted as a function of exposure to the radiation, gave a set of points that could be fitted well with an exponential type of curve.

3. Using the agar plate technique, the colonies arising from organisms receiving varying amounts of radiation were then followed. From this it was learned that the delay observed with the photo-cell instrument was due to organisms being killed by the irradiation rather than injured by it, and that those which survived appeared to be as vigorous as the controls. In regard to the latter, the organisms which survived

behaved as though they had received no treatment whatsoever.

4. Counts were made of the number of colonies arising from samples receiving varying amounts of radiation and a survival curve was plotted from the data obtained. This, likewise, tended toward the exponential type but some question arose in connection with the distribution of the experimental points. However, the complete lack of a sigmoid character in this curve and in the curve obtained with the photo-cell instrument, places the response of *S. cerevisiae* to 200 kv. roentgen rays in the one-hit-to-kill category.

5. Microscopical examinations showed that cells affected lethally may undergo several divisions following exposure, but that they rarely, if ever, go beyond the forty-cell (colony) stage.

We wish to express our appreciation to Dr. G. Failla for his interest and cooperation throughout the course of the work and for his suggestions.

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THE PRODUCTION OF RADIOACTIVE SUBSTANCES AND NEUTRON RAYS*

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IT IS the purpose of this paper to tell something of the recent discoveries and techniques of physics which have given to medicine and biology new and powerful tools whose uses have been described in recent papers.[1] In the limited space available it is necessary to make many statements quite dogmatically. The details of the experimental elucidation of the facts described here can be found in various excellent textbooks and summarizing articles which have appeared recently.[2]

In the closing years of the nineteenth century a series of startling discoveries inaugurated a period of extreme fertility in the physical sciences. These were the discoveries of the electron, x-rays and radioactivity—all phenomena essentially atomic in character. In the next quarter of a century experimental physicists have demonstrated that the atom is a complicated structure consisting of a central body (the *nucleus*), in which nearly all the mass is concentrated, surrounded by one or more swiftly moving electrons. Such a model of the atom, like an infinitesimal solar system, is a very helpful one in visualizing many of its properties. It is a model, however, which is somewhat too simple and in the course of further development it has been found that this analogy cannot be stretched too far. The number of electrons surrounding the nucleus is the same for all the atoms of any one particular chemical element and varies for different elements. The number of electrons, therefore, determines the chemical characteristics of any particular atom, and because of this great importance has been given the name *atomic number*. It has also been found that electricity is also essentially atomic in that no electrical charge smaller than is carried by one electron has ever been found. Since normally an atom is electrically neutral, the nucleus must carry an electrical charge equal and opposite to the total charge of the surrounding electrons. The circumnuclear electrons are negatively charged and consequently the nucleus must be positively charged.

The mass of the nucleus is, in round numbers, the *atomic weight* of the atom. When a chemist measures the atomic weight of an element he is measuring an average of the atomic weights of the various atoms which make up the chemical weight of an element. By this, one must understand that all the atoms of a chemical element do not have the same weight even though they have the same number of surrounding electrons. Thus, chlorine has a chemical atomic weight of 35.457 and is actually made up of two kinds of chemically identical atoms. About 75 per cent of these have a mass of 35 and 25 per cent have a mass of 37. Since the atoms are chemically identical, their outer appearance must be the same. On current views of chemical combination we understand that the chemical properties of an atom depend on the outer electronic structure, and consequently two different nuclei with the same electrical charge will surround themselves with the same number of electrons and will be chemically identical. Such atoms are called *isotopes*.

From these remarks it is obvious that

[1] Lawrence, John. Handbook of Physical Therapy. American Medical Association.

[2] Feather, N. *Nuclear Physics*, Cambridge University Press, 1936. Rasetti, F. *Elements of Nuclear Physics*, Prentice-Hall. 1936. Lord Rutherford, *The New Alchemy*. Bethe, H. A. *Reviews of Modern Physics*, April, 1936, April, 1937, July, 1937.

* Read at the Twenty-Third Annual Meeting, American Radium Society, San Francisco, Calif., June 13–14, 1938.

from the infinite variety of nuclei which we could imagine as having been born in the chaos of creation, only a certain limited number of these have survived on the earth to this day. The ones which did not survive must have represented types which were poorly constructed—they were either too light or too heavy and in the long periods of geologic time those with an unsound architecture have fallen to pieces or disintegrated. This view is further strengthened by the fact that some of these prehistoric monsters actually have survived. All the heavy, naturally radioactive elements such as uranium, thorium and radium belong to this class. It is an everyday experience for a physicist to observe and study the disintegration of these elements since they express their instability by the emission of radiations. Several varieties of these radiations are known and are used daily by medical men. Some nuclei disintegrate by emitting high speed alpha particles (which are identical with the nuclei of helium atoms) others by the emission of beta particles (which are simply swiftly moving electrons). The emission of alpha and beta particles are often accompanied by the emission of gamma rays (similar to but harder than roentgen rays). It is very easy to detect radiations of this type and therefore to find out how many atoms of, say, one gram of uranium are disintegrated per second. This is a very large number, but compared to the number of atoms in the gram of uranium it is sufficiently small for us to understand how uranium has lasted. Indeed, one of the best ways of estimating the age of the earth is from just such measurements as this.

Since the discovery of the *neutron* seven years ago physicists have learned that all nuclei are built up of neutrons and *protons*. The proton is an old friend, having been known for over twenty years, and is simply the nucleus of an ordinary hydrogen atom. It has been found that a neutron has no electrical charge and a proton has a unit positive charge. The charge on the proton then is equal and opposite to the charge on an electron. The proton and neutron have almost identically the same mass and are each about 1,850 times as heavy as an electron. A single proton will attract to itself a single electron forming a hydrogen atom. A combination of one neutron and one proton will also attract to itself a single electron and this will, of course, be chemically indistinguishable from an ordinary hydrogen atom. It will, however, be twice as heavy. The heavy isotope of hydrogen is well known and can be bought pure as a compressed gas in cylinders. It is called *deuterium* and its nucleus is the *deuteron*. A combination of two neutrons and two protons, together with two surrounding electrons, constitutes a helium atom. The nucleus of helium is the alpha particle, is extremely stable, and acts as a secondary building block in nuclei.

To recapitulate: our present idea of the construction of an atom is that it consists of a nucleus surrounded by a certain number of electrons. The number depends upon the chemical properties of the atom. The nucleus has exactly the same electrical charge as the total charge of the electrons, but of opposite sign. The nucleus, too, is composite, being composed of the same number of protons as there are electrons outside and a number of neutrons necessary to give it the proper mass. In the example given above the two kinds of chlorine atoms would be denoted by the symbols Cl^{35} and Cl^{37}. Chlorine has an atomic number of 17, therefore has 17 electrons around its nucleus. The latter has 17 protons and 18 neutrons for Cl^{35} or 20 neutrons for Cl^{37}.

When high speed particles or other radiations pass through solid matter, the effects they produce vary markedly from one to another. Thus swift alpha particles or protons are easily stopped in a fraction of a millimeter of any solid body. This is because of the strong electrical forces between them and the electrons of the atoms composing the solid matter. Because of their smaller mass electrons are slightly

more penetrating. Roentgen rays and gamma rays are much more penetrating. In addition, they have the property of ejecting electrons from the atoms through which they pass. The biological action of these rays is entirely due to these secondary electrons. When neutrons pass through matter they, having no electrical charge, are not clutched at by the electrons of the ambient atoms and so are very penetrating. Only when a neutron strikes a nucleus is it slowed down. Even then the slowing down is small unless the atom is a hydrogen atom. The neutron simply bounces off the heavier nuclei of lead, iron, copper, etc. The cue ball on a billiard table is not greatly slowed down when it bounces off the rail, but soon loses speed when it makes frequent collisions with other balls whose mass is the same as the cue ball. The situation is similar with neutrons—hydrogen-rich substances like water and paraffin are the best absorbers. The biological action of neutrons is due to the destructive action of the knocked-on protons which accompany its path through biological material. That this is much greater than that of roentgen rays is traceable to the much greater destructive ability of a swift secondary proton as compared with a swift secondary electron.

If, now, we admit that only a certain group of all the possible nuclei, which we could imagine as being formed by combinations of neutrons and protons, will be stable, then we must imagine that if by any means whatever we can force two nuclei to coalesce, such as by firing one nucleus at the other at high speed, the resulting composite may break up into two or more nuclei. It may be that these two will be identical with the original nuclei and we cannot tell whether they have coalesced or simply bounced off each other. It may be that the two or more nuclei wil be different from either of the initial nuclei and we will call this a *transmutation*. A great many of these transmutations have been accomplished and are such a commonplace of nuclear physics that they are treated very much as chemical reactions except that only by analogy are they similar to the usual chemical reaction. Thus, the reaction:

$$N^{14}+He^{4}=O^{17}+H^{1}$$

means that alpha particles (He^4) have been shot into nitrogen (N^{14}) and have caused a transmutation in which a proton (H^1) is ejected and a heavy atom of oxygen remains. The superscripts attached to the chemical symbols indicate which isotope of that particular element is being referred to. Nitrogen has two isotopes of masses 14 and 15 of which the lighter predominates. Oxygen has three of masses 16, 17 and 18 of which 16 predominates. The isotope of mass 17 was discovered in the earth's atmosphere several years after it was proved conclusively that it had been made in this experiment.

Since all nuclei have a positive charge they repel each other with enormous forces and in general it is only when the energy with which nuclei are shot together is of the order of a million volts that reactions such as the one above take place. A limited number of such transmutations were discovered using the high-speed alpha particles emitted by radium and its products. Realizing the limited efficacy of these natural particles physicists went to work to devise artificial means of accelerating nuclei to high speeds. With these artificially accelerated projectiles a great many more transmutations were exposed. Other projectiles besides alpha particles were tried, of which one of the most successful was the deuteron.[3]

It was later discovered that occasionally one of the nuclei resulting from a transmutation was different from any of the known stable isotopes. Thus, a reaction took place when aluminum was bombarded by alpha particles as indicated by the following equation:

$$Al^{27}+He^{4}=P^{30}+n^{1}$$

Several months earlier the neutrons result-

[3] Lewis, Livingston and Lawrence. *Phys. Rev.*, 1933, *44*, 55. Lawrence, Livingston and Lewis. *Phys. Rev.*, 1933, *44*, 56.

ing from this disintegration had been observed. It had also been observed that *positive electrons* were also emitted during this disintegration. There was considerable mystery about this for a while before the exact nature of what was going on was discovered. In the first place, it was reasoned that since aluminum and phosphorus have only one isotope something like this must be happening. Furthermore, the positive electron was a newcomer with which people did not feel completely familiar and some thought that the reaction

$$Al^{27}+He^{4}=Si^{30}+H^{1}$$

was occurring, and that somehow the proton was breaking up into a neutron and positive electron on its way out of the nucleus. The astonishing fact was that when the alpha-particle bombardment was stopped positive electrons kept on coming. The number which emerged dropped to half its initial value in two and one-half minutes, to one-quarter of its initial value in five minutes, to one-eighth of its initial value in seven and one-half minutes. If the aluminum was dissolved and a chemical separation for phosphorus made, the positive electrons were found to come from the phosphorus precipitate. By a series of tests like this it was established that the first equation was the correct one, and that the experiment had consisted in creating a new nucleus (P^{30}—ordinary phosphorus has a single isotope of mass 31). It was also clear why this nucleus was not found on the earth because it disintegrated so rapidly that in the course of a few hours none of it would be left. This subsequent disintegration can be expressed in an equation as follows:

$$P^{30}=Si^{30}+e^{+}$$

where e^{+} stands for the positive electron. It was thus made possible to create new atoms which differed in no way from ordinary chemical atoms except for the fact that their nuclei were unstable and emitted penetrating radiations whose hardness was as great or greater than those of the natural radioactive substances. This phenomenon is known as the production of *artificial radioactivity*. It has since been found possible to manufacture more new unstable radioactive elements than there are stable elements. Moreover, it is possible to manufacture them with activities in the neighborhood of that of a gram of radium.

Due to the ease with which the radiations from such artificially produced radioactive substances can be detected even through fair thicknesses of biological material, they have already come into considerable use as tracer elements in metabolism studies as has already been indicated by other papers.[4] It must here again be emphasized that the chemical properties of these radio-elements differ in no way from the chemical properties of their stable sisters.

A great variety of devices have been constructed to speed up atomic particles to such a degree that they may be able to cause transmutations. Of these the most successful so far has been a device known as the *cyclotron*, invented by E. O. Lawrence.[5]

In common with all instruments for accelerating atomic particles the cyclotron makes use of the fact that electrically charged atoms can be accelerated by an electrical field. There are many means of charging or ionizing atoms. In Figure 1 let us assume that there are a large number of ions of the particular sort we wish to accelerate at the point P which is at the center of a large, cyclindrical, air-tight, brass box. In the interior of this brass box are two electrodes A and B made of copper and having a shape very much like half of a pill box. These electrodes are connected to a radiofrequency oscillator so that they are driven alternately positive and negative several million times a second. If the ion is positively charged it will be pulled toward A when A is negatively charged.

[4] See reference 1 and the following as examples: Chievitz, O., and Hevesy, G. *Det. Kgl. Danske Videnskabernes Selskab. Biolog. Meddelelser* XIII, 9 (1937). Hamilton, J. G. *Proc. Nat. Acad.*, 1937, *23*, 521.

[5] Lawrence and Cooksey. *Phys. Rev.*, 1936, *50*, 1131. Kurie. *J. Applied Physics*, 1938, *9*, 691.

If now a large, steady magnetic field is applied perpendicular to the box (and to the plane of the drawing) the ion will be forced to move in a circular path so that after a very short time the ion will return to the gap between the electrodes. If it arrives at the gap in time to find that the charge on *A* has reversed it will be repelled from *A* and consequently gain in speed. The size of the circle in which it travels will now be a little greater but the time

D, pulls the ion away from the center and directs it toward a thin window, *W*, through which it passes into the outside world.

It is this stream of high-speed ions which has the ability to transmute elements placed in its path. Its ability to transmute depends on both its energy and the atomic number of the element being bombarded. The great preëminence of the cyclotron is due entirely to its being the only instru-

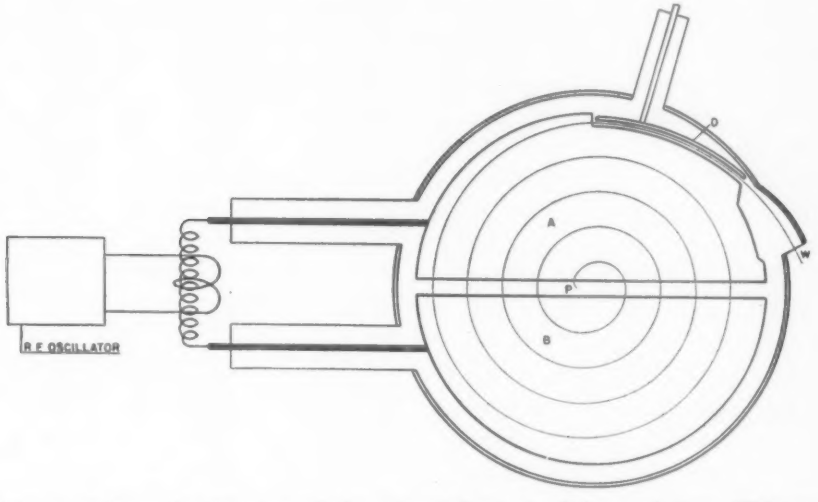

Fig. 1. Schematic diagram of the essential parts of the cyclotron. This represents a cross section of a flat, hollow brass box which is placed between the poles of a strong electromagnet. Inside the box are two D-shaped electrodes between which an electric field is caused to oscillate very rapidly by means of the radiofrequency oscillator shown coupled to the electrode supports at the left. An ion created at *P* will follow a spiral path as shown, until it eventually emerges through the window *W* to be utilized as described in the text. (Republished, with permission, from *General Electric Review*.)

taken for the ion to describe a semicircle will be unchanged so that the ion will swing around crossing the gap in step with the oscillating electrical field so that each time it gains velocity. Obviously, if the maximum potential difference between the electrodes is 100,000 volts the ion will be accelerated to 10,000,000 volts after crossing the gap a hundred times. These repeated accelerations cause the ion to spiral from the center of the apparatus toward the periphery, so that when it attains the maximum energy which the size of the electrodes will allow, it can escape into a region where an electrically charged plate,

ment whereby high-speed ions with energies in excess of 2 million volts have been produced. It is a matter of no particular difficulty to accelerate particles until they have an energy of over 10 million volts. Several cyclotrons are now being constructed which will give particles with an energy of between 15 and 25 million volts.

Apart from the fact that any artificial accelerating device can emit particles of a great many different kinds in contrast to the one kind emitted by naturally radioactive sources and thereby cause transmutations which could not be attained with alpha particles alone, it is interesting to

compare the intensity of the radiation from the cyclotron with that from natural radioactive sources. The number of high-speed particles emitted per second from a cyclotron is usually measured in micro-amperes. If these particles are singly charged (protons or deuterons) one micro-ampere represents the total number of alpha particles emitted by 40 grams of radium. This is about one-twentieth of the total supply of radium in hospitals, laboratories, etc., in the whole world. A comparatively small cyclotron (such as the 37-inch installation at the University of California) can easily produce about 80 microamperes at 8 million volts. The new 60-inch cyclotron at the University of California which has recently been completed has been able to produce many times these numbers. With the 37-inch cyclotron it is, for example, possible to make 70 millicuries of radiosodium per hour. Thus, in a good long day's work, a radioactive sample as strong as one gram of radium can be made. The artificial radioactive sources are, with good technique, every bit as concentrated as radium itself. Since one millicurie represents the activity of one milligram of radium, the fact that radiophosphorus samples have been prepared with a strength of 36 millicuries per milligram of phosphorus is an eloquent demonstration of this.

The production of neutrons is simply another type of transmutation in which some substance is bombarded by high speed particles. The most prolific nuclear reaction thus far known is the bombardment of beryllium with swift deuterons in accordance with the reaction:

$$Be^9 + H^2 = B^{10} + n^1$$

With 80 microamperes of 8 million volt deuterons the yield of neutrons is sufficiently great to give a tissue dose comparable to that from a standard treatment roentgen-ray tube. A neutron dose is frequently measured in n units instead of the familiar roentgen. At 70 cm. skin-target distance and with a 3 cm. lead filter the 37-inch Berkeley cyclotron gives 240 n per hour; 200–250 n gives a skin reaction similar to that following 1,300 r of 200 kv. x-rays. One n-unit is equivalent to about 2.5 r x-rays in tissue ionization, and according to present experimental evidence is about six times as biologically effective as 1 r of x-rays.

Recent improvements in cyclotron technique have been responsible for great increases in the yield of both radioactive materials and neutron rays. The figures given in this paper by no means represent the ultimate yield of the instrument.

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Delegates to the Sixth International Congress of Radiology: Albert Soiland, Los Angeles, Calif., Delegate, Zoe A. Johnston, Pittsburgh, Pa., Alternate Delegate.

Twenty-fifth Annual Meeting: New York City, June 10–11, 1940.

EDITORIAL

FIBROCYSTIC DISEASE OF BONE

FOLLOWING the demonstration of the relation existing between disturbances of the parathyroids and the diffuse fibrocystic disease of bone, often referred to as von Recklinghausen's disease, a great deal of attention has been given to the recognition of these cases and to the benefit which might be derived from parathyroidectomy. These studies were greatly stimulated by those of Aub and Hunter, particularly their work on calcium and phosphorus metabolism in relation to fibrocystic disease, and as a result a widespread interest in cystic disease of bone in general has been awakened.

Out of all of this maze of reports and investigation it has been clearly demonstrated that not all of the diffuse cystic changes in the skeleton are due to parathyroid disturbances and not all of them are benefited by parathyroidectomy. Wilder and Howell, from a study of 135 proved cases, gave the following as the invariable features of this group which apparently are not associated with parathyroid disease as an etiological factor: In order to make an indisputable diagnosis of osteitis fibrosa cystica there must be the skeletal appearances typical of this disease; there must be indisputable abnormality of calcium metabolism demonstrated by a study of the blood or urine, and there must be tumorous enlargement of one or more parathyroids. Later, however, Gutman and his coworkers suggested that evidence of disturbed calcium metabolism will not necessarily always accompany even true fibrocystic disease of the skeleton associated with parathyroid tumor. They pointed out that a normal blood calcium figure may often be found in such cases in the presence of renal failure and that from experimental evidence variations in calcium intake may possibly be of importance and also that the disease may be subject to spontaneous remissions.

Hunter some time ago pointed out that roentgenographically there are skeletal changes simulating osteitis fibrosa cystica where there is a multiple focal type of fibrocystic disease and that these skeletal changes may occur without parathyroid tumor.

Recently Robson and Todd[1] reported a case of fibrocystic disease of bone with extensive skin pigmentation and endocrine dysfunction. Previous to the reports of Robson and Todd, Albright and others described a syndrome characterized by osteitis fibrosa disseminata with areas of skin pigmentation and endocrine dysfunction with precocious puberty in females and in none of the cases which Albright reported was there evidence of a parathyroid tumor. The cases reported by Albright, Robson and Todd, and others, have as the chief feature of their syndrome an extensive osseous dystrophy of the fibrocystic type, either generalized or unilateral, pigmentation of the skin and in girls precocious sexual development. The clinical picture has a striking resemblance to hyperparathyroidism, though there is no negative calcium balance and in exploration of some of these cases no parathyroid tumors have been found.

The roentgenographic appearance of the skeleton, particularly in advanced cases, is indistinguishable from that seen in true types of fibrocystic disease of bone associated with hyperparathyroidism. One striking characteristic of the skeletal changes is the tendency to a unilateral involvement of the skeleton.

[1] Robson, K., and Todd, J. W. Fibrocystic disease of bone. *Lancet*, 1939, *1*, 377–380.

Robson and Todd, in a discussion of their case which bore great similarity to previous cases reported, suggested that the bizarre association of bone changes with cutaneous pigmentation and precocious puberty in the females might point to the condition being a specific entity and that possibly the male cases, in which no precocious puberty occurs, should be regarded as distinct from the female.

McCune and Bruch[2] reported a case of a Jewish girl of nine who exhibited true precocious puberty, asymmetrically distributed fibrocystic osteodystrophy of a progressively incapacitating nature and unchanging pathologic pigmentation of the skin. These features had been manifested in their case since the second year of the patient's life. The plasma phosphatase activity was increased; in other respects, however, numerous clinical examinations of the blood gave normal results and the calcium and phosphorus metabolic studies gave findings similar to those obtained for healthy children. The patient showed no hypercalciuria, and biopsy of the bone provided no clearcut information concerning the precise classification or the etiology of the osseous dystrophy. In their studies they were able to gather from the literature and other sources eight, possibly nine, females with an identical condition and five males showing fibrocystic osteodystrophy and pathologic pigmentation of the skin but not precocious puberty and they concluded that there is some question as to whether the condition of the males and that of the females are fundamentally related. These unusual skeletal changes associated with pigmentation of the skin and apparently unassociated with parathyroid tumor suggest an identical etiological factor but a careful study of all of the available evidence relating to the collected cases gives no exact information concerning the nature of the factor.

Braid,[3] who was probably the first to record such a condition in the male, advanced the opinion that the bone dystrophy is due to some impairment of the function of the liver, possibly a mechanism concerned with the storage and utilization of vitamins.

The striking clinical and roentgenological manifestations in these cases is a challenge to further study in order to arrive at the underlying etiological factor and all cases presenting such clinical and skeletal changes and demonstrated roentgenographically should be adequately studied and reported in the hope that in the accumulation of evidence there might be brought about an elucidation of the causal factor. Whether it is, as Braid suggests, liver disturbances concerned with the utilization of vitamins or a disease of endocrine imbalance remains to be proved. While it may be a clinical entity, its striking similarity in many respects to von Recklinghausen's disease cannot be denied.

[2] McCune, D. J., and Bruch, H. Osteodystrophia fibrosa. *Am. J. Dis. Child.*, 1937, *54*, 806–848.

[3] Osseous dystrophy following icterus neonatorum. *Lancet*, 1939, *2*, 798.

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

Items for this section solicited promptly after the events to which they refer.

MEETINGS OF ROENTGEN SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. C. B. Peirce, Royal Victoria Hospital, Montreal, Canada. Annual Meeting: Boston, Mass., Oct. 1-4, 1940.

AMERICAN COLLEGE OF RADIOLOGY
Secretary, Mac F. Cahal, 540 N. Michigan Ave., Chicago, Ill. Next Annual Meeting: New York City, June 12, 1940.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. J. T. Murphy, 421 Michigan St., Toledo, Ohio. Annual meeting: New York City, June 10–14, 1940.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary, Dr. D. S. Childs, 607 Medical Arts Bldg., Syracuse, N. Y. Annual meeting, 1940: To be announced.

RADIOLOGICAL SECTION, BALTIMORE CITY MEDICAL SOCIETY
Secretary, Dr. Walter L. Kilby, Baltimore. Meets third Tuesday each month, September to May.

RADIOLOGICAL SECTION, CONNECTICUT MEDICAL SOCIETY
Secretary, Dr. Max Climan, 242 Trumbull St., Hartford, Conn. Meets twice annually in May and September.

SECTION ON RADIOLOGY, ILLINOIS STATE MEDICAL SOCIETY
Secretary, Dr. H. W. Ackemann, 321 W. State St., Rockford, Ill. Next meeting Peoria, Ill., May 21–23, 1940.

RADIOLOGICAL SECTION, LOS ANGELES CO. MED. SOC.
Secretary, Dr. Wilbur Bailey, 2007 Wilshire Blvd., Los Angeles, Calif. Meets on second Wednesday of each month at County Society Building.

RADIOLOGICAL SECTION, SOUTHERN MEDICAL ASSOCIATION
Secretary, Dr. Roy G. Giles, Temple, Texas.

BROOKLYN ROENTGEN RAY SOCIETY
Secretary, Dr. L. J. Taormina, 1093 Gates Ave., Brooklyn, N. Y. Meets monthly on first Tuesday, October to April.

BUFFALO RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Joseph S. Gian-Franceschi, 610 Niagara St., Buffalo, N. Y. Meets second Monday of each month except during summer months, place of meeting selected by the host.

CHICAGO ROENTGEN SOCIETY
Secretary, Dr. C. J. Challenger, 3117 Logan Blvd. Meets second Thursday of each month October to May inclusive at the Hotel Sherman.

CINCINNATI RADIOLOGICAL SOCIETY
Secretary, Dr. J. E. McCarthy, 707 Race St., Cincinnati, Ohio. Meets third Tuesday of each month, October to May, inclusive.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary, Dr. H. A. Mahrer, 10515 Carnegie Ave. Meets at 6:30 P.M. at Mid-Day Club rooms on fourth Monday each month, October to April, inclusive.

DENVER RADIOLOGICAL CLUB
Secretary, Dr. E. A. Schmidt, 4200 E. 9th Ave., Denver, Colo. Meets third Tuesday of each month.

DETROIT ROENTGEN RAY AND RADIUM SOCIETY
Secretary, Dr. E. R. Witwer, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne County Medical Society Building.

FLORIDA STATE RADIOLOGICAL SOCIETY
Secretary, Dr. J. N. Moore, 210 Professional Bldg., Ocala, Florida. Meetings in May and November.

GEORGIA RADIOLOGICAL SOCIETY
Secretary, Dr. R. C. Pendergrass, Prather Clinic Bldg., Americus, Ga. Meets in November and at annual meeting of Medical Association of Georgia in the spring.

ILLINOIS RADIOLOGICAL SOCIETY
Secretary, Dr. E. P. Halley, Decatur and Macon County Hospital, Decatur, Ill. Meetings held quarterly, time and place designated by president.

INDIANA ROENTGEN SOCIETY
Secretary, Dr. C. C. Taylor, 23 E. Ohio St., Indianapolis, Ind. Meeting held the second Sunday in May annually.

KENTUCKY RADIOLOGICAL SOCIETY
Secretary, Dr. J. C. Bell, 402 Heyburn Bldg., Louisville. Meets annually in Louisville on third Sunday afternoon in April.

LONG ISLAND RADIOLOGICAL SOCIETY
Secretary, Dr. Marcus Wiener, 1430-48th St., Brooklyn, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:30 P.M.

MICHIGAN ASSOCIATION OF ROENTGENOLOGISTS
Secretary, Dr. C. S. Davenport, St. Lawrence Hospital, Lansing. Three meetings a year, Fall, Winter, Spring.

MILWAUKEE ROENTGEN RAY SOCIETY
Secretary, Dr. I. I. Cowan, Mt. Sinai Hospital, Milwaukee, Wis. Meets monthly on first Friday at University Club.

MINNESOTA RADIOLOGICAL SOCIETY
Secretary, Dr. J. P. Medelman, 572 Lowry Medical Arts Bldg., St. Paul.

NEBRASKA RADIOLOGICAL SOCIETY
Secretary, Dr. D. A. Dowell, Medical Arts Bldg., Omaha, Nebr. Meets first Wednesday of each month, at 6 P.M., at either Omaha or Lincoln.

NEW ENGLAND ROENTGEN RAY SOCIETY
Secretary, Dr. A. O. Hampton, Massachusetts General Hospital, Boston, Mass. Meets monthly on third Friday, Boston Medical Library.

RADIOLOGICAL SOCIETY OF NEW JERSEY
Secretary, Dr. W. J. Marquis, 198 Clinton Ave, Newark. Meets annually at time and place of State Medical Society. Mid-year meetings at place designated by president.

NEW YORK ROENTGEN SOCIETY
Secretary, Dr. R. D. Duckworth, 170 Maple Ave., White Plains, N. Y. Meets monthly on third Monday, New York Academy of Medicine, at 8:00 P.M.

NORTH CAROLINA ROENTGEN RAY SOCIETY
Secretary, Dr. Major Fleming, Rocky Mount, N. C. Annual meeting at time and place of State Medical Society. Mid-year scientific meeting at place designated.

CENTRAL NEW YORK ROENTGEN RAY SOCIETY
Secretary, Dr. C. F. Potter, 820 S. Crouse Ave., Syracuse. Three meetings a year—January, May, November.

PACIFIC ROENTGEN CLUB
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

PENNSYLVANIA RADIOLOGICAL SOCIETY
Secretary, Dr. L. E. Wurster, 416 Pine St., Williamsport, Pa. Annual meeting, June, 1940, exact time and place to be decided.

PHILADELPHIA ROENTGEN RAY SOCIETY
Secretary, Dr. B. R. Young, Temple University Hospital. Meeting first Thursday of each month from October to May inclusive, at 8:15 P.M., in Thompson Hall, College of Physicians, 19 S. 22d St

PITTSBURGH ROENTGEN SOCIETY
Secretary, Dr. H. W. Jacox, 4800 Friendship Ave., Meetings held second Wednesday each month, 4:30 P.M., October to June at various hospitals.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y.
Secretary, Dr. S. C. Davidson, 277 Alexander St., Meets on second Thursday from October to May, inclusive, 8 P.M., Rochester Academy of Medicine Building.

ST. LOUIS SOCIETY OF RADIOLOGISTS
Secretary, Dr. W. K. Mueller, University Club Bldg. Meets fourth Wednesday of October, January, March and May, at a place designated by the president.

SAN FRANCISCO RADIOLOGICAL SOCIETY
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco. Meets monthly on first Monday at 7:45 P.M., alternately at Toland Hall and Lane Hall.

* Secretaries of Societies not here listed are requested to send the necessary information to the Editor.

South Carolina X-Ray Society
Secretary, Dr. Hillyer Rudisill, Jr., Roper Hospital, Charleston. Meets in Charleston on first Thursday in November, also at the time and place of South Carolina State Medical Association.

Tennessee Radiological Society
Secretary, Dr. F. B. Bogart, 311 Medical Arts Bldg. Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. H. C. Harrell, 517 Pine St., Texarkana, Texas.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets every Thursday from 4:00–5:00 P.M., Room 301, Service Memorial Institute.

Virginia Radiological Society
Secretary, Dr. V. W. Archer, University Hospital, University, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. K. J. Holtz, American Bank Bldg., Seattle. Meets fourth Monday of each month at the College Club, Seattle.

Cuba

Sociedad Cubana de Radiologia y Fisioterapia
Secretary, Dr. Francisco Padron, Enrique, Villuendas 64, Havana, Cuba. Meets monthly in Havana.

British Empire

British Institute of Radiology Incorporated with the Röntgen Society
Meets monthly on third Thursday, from November to June inclusive, at 8:15 P.M., 32 Welbeck St., London.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets on the third Friday of each month during the winter at 8:15 P.M. at the Royal Society of Medicine, 1, Wimpole St., London, W. 1.

Faculty of Radiologists
Secretary, Dr. Barbara M. Key, 32 Welbeck St., London, W.1, England.

Section of Radiology and Medical Electricity, Australasian Medical Congress
Secretary, Dr. H. M. Cutler, 139 Macquarie St., Sydney, New South Wales.

Radiological Section of the Victorian Branch of the British Medical Association
Secretary, Dr. Keith Hallam, St. George's Hospital, K.E.W., Melbourne, E. 4, Victoria, Australia. Meets monthly from March to Nov. incl. for scientific discussion.

Canadian Association of Radiologists
Secretary, Dr. A. C. Singleton, Medical Arts Bldg., Toronto, 5, Ontario.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext., Halifax, N.S.

Radiological Section, New Zealand British Medical Association
Secretary, Dr. Colin Anderson, Invercargill, New Zealand. Meets annually.

Continental Europe

Belgian Society of Roentgenology
Secretary, Dr. J. Boine, Avenue des Ailiés, 134, Louvain (Belgium).
Meets monthly on second Sunday at d'Egmonds Palace, Brussels, except in the summertime.

Sociedad Espanola de Radiologia y Electrologia
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7, Madrid, Spain. Meets monthly in Madrid.

Société de Radiologie Médicale de France
Meets monthly on second Tuesday, except during months of August and September, 12 Rue de Seine, Paris.

Société Suisse de Radiologie (Schweizerische Röntgen-Gesellschaft)
Secretary for French language, Dr. A. Grosjean, La Chaux de Fonds.
Secretary for German language, Dr. Scheurer, Molzgasse, Biel. Meets annually in different cities.

Société Francaise d'Electrothérapie et de Radiologie Médicale
Meets monthly on fourth Tuesday, except during month of August and September, 12 Rue de Seine, Paris.

Association of German Roentgenologists and Radiologists in Czecho-Slovakia
Secretary, Dr. Walter Altschul, German University, Prague, II.52.

Deutsche Röntgen-Gesellschaft (Gesellschaft für Röntgenkunde und Strahlenforschung)
Meets annually in April, alternating one year in Berlin, one year in some other German city. Meets in addition every two years with the Gesellschaft deutscher Naturforscher und Aerzte.
Permanent Secretary, Professor Dr. Haenisch, Klopstockstrasse 10, Hamburg, Germany.

Süd- und Westdeutsche Röntgensellschaft
Meets annually in different cities.

Nord- und Ostdeutsche Röntgengesellschaft
Meets annually in different cities.

Dutch Society of Electrology and Roentgenology
Holds two meetings a year in Amsterdam, one in the Spring, and one in the fall.

Societa Italiana Radiologia Medica
Secretary, M. Ponzio, University of Turin, Prof. Turin

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banul Mărăcine, 30, S. I., Bucuresti, Roumania.
Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad, USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Leningrad Roentgen Ray Society
Secretaries, Drs. S. G. Simonson and G. A. Gusterin. Meets monthly, first Monday at 8 o'clock State Institute of Roentgenology and Radiology, Leningrad.

Moscow Roentgen Ray Society
Secretaries, Drs. L. L. Holst, A. W. Ssamygin and S. T. Konobejevsky. Meets monthly on first Monday at 8 o'clock.

Polish Society of Radiology
Secretary, Dr. Jan Kochanowski, 45 Gornoslazka St., Warsaw. Meets annually.

Warsaw Section, Polish Society of Radiology
Secretary, Dr. B. Krynski, 11 Zielna St.
Meets once a month except in the summertime.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association. Each of the following societies, with exception of the Denmark Society, meets every second month except in the summertime:

Society of Medical Radiology in Sweden
Meets in Stockholm.

Society of Medical Radiology in Norway
Meets in Oslo.

Society of Medical Radiology in Denmark
Secretary, Dr. G. Biering, Copenhagen.
Meets the second Wednesday of each month from October to July in Copenhagen, at 8 o'clock in the State Institute of Roentgenology.

Society of Medical Radiology in Finland
Meets in Helsingfors.

Vienna Roentgen Society
Meets first Wednesday of each month, at 6:30 P.M. at Zentral-Röntgen Institut des allgemeinen Krankenhauses Alserstrasse 4.

Orient

Japan X-Ray Association
c/o Orthopedic Surgery, Tokyo Imperial University. Meets annually in April.

Kinki Roentgen-Abend Society
Director, Dr. Prof. Taiga Saito, Ogawaoike Tyoto Japan. Meets bi-monthly on third Sunday.

REPORT OF THE RESEARCH AND STANDARDIZATION COMMITTEE OF THE AMERICAN RADIUM SOCIETY

THE effort made by this Committee in 1937 to collect information concerning methods used by members of the American Radium Society for treatments of carcinoma of the uterine cervix indicated a wide variation in methods both concerning the general plan of the treatments and the dose used. The progress in radium therapy has been considerable, but it is evident that no agreement has as yet been reached concerning the most efficacious method. Any attempt of this Committee to advocate certain types of treatments or to specify the dosage for any type of disease would therefore simply represent the opinions of its members.

The importance of the time distribution of the irradiation as particularly emphasized by Regaud and Coutard has been generally accepted. The complicated relations between the time factor and the biological effects are so difficult to determine that our knowledge in this field is still very limited in spite of many valuable investigations and observations. Though careful consideration of time distribution has led to improved results from treatments, it is impossible as yet to state accurately which time distribution would be the best one for treatment of a certain disease.

It is evident that the distribution of the radiation throughout the treated area must be carefully considered and that the determination of the total dose of radiation at different portions of the tissues as well as the rate of dose is of fundamental importance. Certain measurements and calculations have been made which are accurate enough to permit a general acceptance.

For the reasons given we have confined ourselves in this report to the consideration of the physical factors of radium and radon therapy. It seemed advisable to collect some data from publications during the last few years and arrange a set of reliable tables which would be useful for the members of the Society. Between 1926 and 1930 the Society published the reports of the Research and Standardization Committee on loose leaves which could be assembled in folders. We wish to propose that this action be renewed. It seems, however, practical to make the loose leaves the same size as the Journal so that the same can be used both for publication in the Journal and the loose leaves. The old loose leaves were of smaller size, but they are now out of date, and the new tables are more accurate and complete and should therefore replace the old ones.

It would take too long a time to discuss the tables in detail, but some lantern slides will give an idea of the material. A few copies are available for those who desire to examine it in detail. We hope the Society will accept the full report for publication in the Journal and in a loose leaf form.

Physical Factors for Therapy with Radioactive Substances

When treatments are given with radium or radon, it is advisable to give the following factors:

(1) Amount of radium in milligrams or radon in millicuries.

(2) The time of exposure in hours (days or minutes).
When radon implants are used and not removed, it is enough to give the number of millicuries per implant and the total number of implants as such a source always irradiates the same length of time. The total number of millicurie hours is 133 times the number of millicuries.
When the dose is split between several applications, the length of each treatment and the time interval between treatments should be given.

(3) The kind and thickness of filter used.

(4) The surface area over which the radium is spread.
If the individual applicators are placed some distance apart, the configuration should be described. If the irradiating

layer is more than 1 mm. thick (e.g. tubes placed on top of each other), the thickness should also be given.

(5) The distance from the center of the applicator to the nearest point of the tissues (skin) should be accurately stated.

(6) The three dimensions of the irradiated mass.
This information is of special importance when interstitial irradiation is used.

(7) The approximate distribution of the sources within the tissues should also be outlined.

These factors give information which can be used for the calculation of the dose at the surface as well as at certain depths. The dose received by a small volume of tissue can be given in threshold erythema doses. It is, perhaps, more convenient to express this dose in a concise physical unit. The roentgen has been used for this purpose and is adopted in the following tables. It must be kept in mind that this unit as here defined may not cause the same effect as 1 r of roentgen rays, and the γ-ray r is, therefore, specified as r_γ. A number of careful measurements carried out at different laboratories indicate that the following value is fairly accurate and the best obtainable at the present time.

A point source of 1 mg. of radium filtered with 0.5 mm. of platinum gives a dose of 8.3 r_γ in one hour at a distance of 1 cm. If this value is accepted, it can be stated that 1,000 r_γ given in less than two hours approximately corresponds to a threshold erythema dose.

TABLE I*

RELATIVE AMOUNTS OF RADIATION TRANSMITTED BY VARIOUS FILTERS†

Metal	Thickness mm.	Amount of Radiation Relative to 0.5 mm. Pt	Composition of Radiation	
			Beta (per cent)	Gamma (per cent)
Brass	0.5	160	33	67
	1.0	111	8	92
	2.0	100	0	100
	3.0	95	0	100
	4.0	92	0	100
Silver	0.5	128	17	83
	1.0	103	0	100
	2.0	94	0	100
	3.0	90	0	100
Lead	0.5	118	12	88
	1.0	97	0	100
	2.0	88	0	100
	3.0	83	0	100
Gold or platinum	0.2	135	22	78
	0.3	111	9	91
	0.5	100	0	100
	1.0	88	0	100
	1.5	82	0	100
	2.0	78	0	100
	3.0	73	0	100

* From Quimby.[9]
† Metal filter only; no secondary filter used.

TABLE II

(Calculated from Table 1)

CORRECTION FACTOR FOR ADDITIONAL FILTRATION ABOVE 0.5 MM. PT

Additional Thickness of Metal	Brass Steel Monel	Silver Lead	Gold Platinum
0.5	1.03	1.05	1.14
1.0	1.05	1.10	1.22
1.5	1.07	1.13	1.28
2.0	1.09	1.16	1.33
2.5			1.37

A. *Filters.*

1. When β-rays are used for treatments the filtration must be light. Small variations in the material may influence the dose considerably. No satisfactory standards have been worked out. It is best to determine empirically suitable dosage for each applicator used. The dose falls off rapidly in the tissues and as an approximation it may be assumed that 75 per cent of the β-rays are absorbed by the first 2 mm. of tissue and 15 per cent in the next 2 mm.

2. As a simple rule it may be stated that the primary β-rays are removed by

2 mm. of brass, copper, steel or monel metal
1 mm. of lead or silver
0.5 of platinum or pure gold.

TABLE III

(The values of this table have been calculated)

NUMBER OF γ-RAY ROENTGENS IN CENTER OF FIELD OBTAINED WITH 1 MG. IN ONE HOUR AT VARIOUS DISTANCES FROM VARIOUS FLAT APPLICATORS

Distance cm.	Radium Evenly Distributed								
	Tubes				Circles				
	Length cm.				Diameter cm.				
	0	1	2	4	1	2	4	6	8
0.5	33.2	25.1	18.3	11.0	23.0	13.4	5.87	3.33	2.16
1.0	8.3	7.7	6.55	4.51	7.4	5.75	3.34	2.12	1.47
2.0	2.07	2.03	1.92	1.63	2.02	1.85	1.43	1.09	0.835
3.0	0.923	0.908	0.888	0.815	0.916	0.873	0.763	0.639	0.534
5.0	0.332	0.330	0.327	0.316	0.332	0.325	0.307	0.283	0.257

Radium Placed at the Periphery Only

WHEN THE DIAMETER OF APPLICATOR IS LARGER THAN TWICE THE DISTANCE, THE MAXIMUM DOSE IS REACHED SOME DISTANCE FROM THE CENTER OF THE FIELD AND IS LARGER THAN THE FIGURES IN THE TABLE.

Distance cm.	Circles					Squares				
	Diameter cm.					Length of sides cm.				
	1	2	4	6	8	1	2	4	6	8
0.5	16.60	6.64	1.95	.90	.51	14.3	5.43	1.55	.710	.404
1.0	6.64	4.15	1.66	.83	.49	6.20	3.65	1.35	.670	.389
2.0	1.95	1.66	1.05	.64	.42	1.93	1.55	.907	.531	.340
3.0	0.90	0.83	0.64	.46	.33	.89	.80	.585	.401	.280
5.0	0.33	0.32	0.29	.24	.20	.33	.32	.274	.225	.181

Rectangles

Distance cm.	1×2	2×4	4×6	6×8
0.5	9.9	3.98	1.13	.557
1.0	4.9	2.50	1.01	.485
2.0	1.74	1.23	.719	.436
3.0	.85	.69	.493	.340
5.0	.33	.30	.250	.203

Table 1 gives the relative amounts of radiation transmitted by various filters.

3. Gamma rays produce secondary β-rays in the filter. The intensity of these rays is a minimum in substances of intermediate atomic number. It therefore should be an advantage to have the outside wall of the container which comes in contact with the tissues made of brass, copper, monel metal, steel or nickel. If a small diameter is essential containers made of platinum or pure gold with a 0.5 mm. thick

wall are best. These can be placed inside capsules made from one of the other metals mentioned if space is available. The increased distance between the radium and the tissues contributes to protection of the surface and to an increased relative depth dose. The γ-ray intensity is reduced as the filter is increased. Thus, it takes 37 per cent longer time to give the same dose with radium filtered through 3 mm. of platinum than with the same amount of radium filtered through 0.5 mm. of platinum (Table II). The increase in penetration of the radiation in tissues is very small when the filter is increased from 0.5 to 3.0 mm. of platinum.

The number of milligram-hours (or the time) calculated for 0.5 mm. Pt filter should be multiplied by the factor found in this table in order to obtain the same dose when the corresponding filter has been added.

B. *Surface Dose.*

The dose at the surface obtained with 1 mg. of radium in one hour depends upon the distance as well as upon the distribution of the radium. Table III gives the number of γ-ray roentgens obtained at the surface without back-scattering for different distances and different distribution of the radium.

C. *Depth Dose.*

The relative depth dose expressed in per cent of the surface dose is given for a few applicators, based upon measurements made by Quimby and Failla.* The distance from applicator to surface is short. The errors introduced because of the size and shape of the ionization chamber, etc., may therefore be considerable, and the accuracy is not as great as in depth dose charts for roentgen rays where the distances are larger. The filter used for the measurements was equivalent to 0.5 mm. platinum. It is evident that the values can be used for heavier filters also as the depth dose does not increase to an appreciable extent when the filter is increased up to 3 mm. of platinum. Table IV refers to applicators with the radium evenly distributed over the surface. Under the same conditions but with the radium placed only at the periphery, a greater number of milligram-hours should be required to produce the same skin reaction and the depth dose should be greater than the values in the table.

When radium tubes are used in cavities, the dose in the tissue falls off rapidly at increasing distances from the applicator. It is then necessary to give a large dose to the surface in order to apply an appreciable dose at 1 cm. depth. It is evident that the

Table IV

PERCENTAGE DEPTH DOSES FOR RADIUM APPLICATORS

Filter 0.5 mm. Pt

Depth cm.	Area of Applicator—sq. cm. 2	5	20	50
	Radium-Skin Distance—cm. 1	2	3	6	10
0	100	100	100	100	100
0.5	44	68	77	85	89
1	28	52	62	75	81
2	13	30	43	62	69
3	4	20	31	51	59
5		9	19	36	44
7			12	25	33
10			4	20	25

Table V*

RELATIVE INTENSITIES OF RADIATION FROM INTRACAVITARY APPLICATORS OF DIFFERENT DIAMETERS, IN FIRST CENTIMETER OF TISSUE

Filter 0.5 mm. Pt and 0.5 mm. Monel
(This table is for needles 4 cm. long. For other lengths the values would be different)

Distance from Surface mm.	Outside Diameter—mm. 3.0	5.0	7.0
	Relative Intensity of Radiation		
0	100	100	100
1	57	66	74
3	28	39	46
5	17	25	33
7	12	20	27
10	9	14	20

* From Sievert.[13]

* Chapter on Radium Dosimetry. The Science of Radiology. Edited by O. Glasser. Charles C Thomas, Springfield, Illinois, 1933.

TABLE VI
(Calculated)

MG-HR. OR MC-HR. NECESSARY TO DELIVER 1 T.E.D. (1,000 r_γ) AT DIFFERENT DISTANCES FROM SOURCES OF VARIOUS LENGTHS

Filter—0.5 mm. Pt

Distance* cm.	Active Length—cm. 0.5	1.0	2.0	4.0	6.0
	mg- or mc-hr. for 1 T.E.D.				
0.5	35	45	60	100	140
1.0	135	150	180	250	340
2.0	540	570	600	700	780
3.0	1160	1180	1225	1350	1500

* The distance is measured along a line perpendicular to the source at its center.

same dose at 1 cm. depth can be obtained with a relatively smaller surface dose if the tube is placed in a capsule of suitable light material so that the diameter of the applicator is increased. Table V gives the relative dose in the tissues at 0 to 10 mm. distance from the surface of applicators of different diameters. If the same dose were applied at 1 cm. depth with such applicators the dose in the first millimeter of tissue would be about twice as large with the applicator 3 mm. thick as with the applicator 7 mm. thick.

The number of milligram- or millicurie-hours required to deliver 1,000 r_γ to different distances from 0.5 mm. platinum needles placed in tissues is given in the following table for needles of various active lengths.

Quantities of Radiation Necessary to Deliver Specified Minimum Doses in Various Tissue Volumes

In Table VI it can be seen that 1,000 r_γ is obtained in the tissues at 1 cm. distance from a 5 mm. long needle with 0.5 mm.

TABLE VII*

QUANTITIES OF RADIATION NECESSARY TO DELIVER SPECIFIED MINIMUM DOSES IN VARIOUS TISSUE VOLUMES

Interstitial Sources — Filter 0.3–0.5 mm. Pt

	Diameter of Spherical Mass—cm. 1	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
	Volume of Mass—Cubic Centimeters 0.5	2	4	8	15	25	35	50	65	90	115
T.E.D.	Milligram- or Millicurie-Hours to Deliver Specified Dose										
1	35	80	135	250	330	420	540	680	830	1000	1160
2	70	160	270	500	660	840	1080	1360	1660	2000	2320
3	105	240	405	750	990	1260	1620	2040	2490	3000	3480
4	140	320	540	1000	1320	1680	2160	2720	3320	4000	4640
5	175	400	675	1250	1650	2100	2700	3400	4150	5000	5800
7	245	560	945	1750	2310	2940	3780	4760	5810	7000	8120
10	350	800	1350	2500	3300	4200	5400	6800	8300	10,000	11,600
	Millicuries-Destroyed to Deliver Specified Dose										
1	0.25	0.6	1.0	1.9	2.5	3.2	4.0	5.0	6.2	7.5	8.7
2	0.5	1.2	2.0	3.8	5.0	6.4	8.0	10.0	12.0	15.0	17.0
3	0.75	1.8	3.0	5.7	7.5	9.6	12.0	15.0	18.0	22.0	26.0
4	1.0	2.4	4.0	7.6	10.0	13.0	16.0	20.0	25.0	30.0	35.0
5	1.25	3.0	5.0	9.5	12.0	16.0	20.0	25.0	31.0	38.0	44.0
7	1.75	4.2	7.0	13.0	18.0	23.0	28.0	35.0	43.0	52.0	61.0
10	2.50	6.0	10.0	19.0	25.0	32.0	40.0	50.0	62.0	75.0	87.0

* Syllabus of Lectures—The Physical Basis of Radiation Therapy. Edith H. Quimby, Memorial Hospital, New York City, 1939.

TABLE VIII*

DECAY OF RADON AND ENERGY EMITTED DURING DECAY

Time		Per Cent Remaining	Mc-hr. per Initial mc.	Time		Per Cent Remaining	Mc-hr. per Initial mc.
Days	Hours			Days	Hours		
0	0	100	0	2	20	59.82	53.42
	2	98.50	1.99	3	0	58.05	55.80
	4	97.02	3.96	3	6	55.47	59.26
	6	96.67	5.90	3	12	53.01	62.44
	8	94.14	7.82	3	18	50.71	65.60
0	10	92.72	9.62	4	0	48.42	68.60
	12	91.33	11.52	4	8	45.60	72.41
	14	89.98	13.33	4	16	43.57	75.07
	16	88.61	15.11	5	0	40.43	79.30
	18	87.28	16.96	5	8	38.02	82.52
0	20	85.98	18.64	5	16	35.78	85.40
	22	84.96	20.38	6	0	33.70	88.40
1	0	83.42	22.08	6	12	30.80	92.15
1	3	81.55	24.55	7	0	28.11	95.78
1	6	79.72	26.97	7	12	25.67	99.00
1	9	77.93	29.35	8	0	23.45	102.1
1	12	76.18	31.70	9	0	19.56	107.0
1	15	74.48	33.98	10	0	16.32	111.4
1	18	72.81	36.16	11	0	13.61	118.0
1	21	71.18	38.38	12	0	11.35	118.0
2	0	69.59	40.45	14	0	7.90	122.5
2	4	67.52	43.20	17	0	4.59	125.8
2	8	65.50	45.91	20	0	2.66	129.4
2	12	63.55	48.51	25	0	1.07	131.5
2	16	61.66	51.00	30	0	0.43	132.5

* International Radium Standards Commission. *J. Am. Chem. Soc.*, 1931, *53*, 2437–2451.

platinum wall if 135 mg-hr. are used. It is therefore evident that the periphery of a spherical mass of tissue 2 cm. in diameter receives approximately 1,000 r_γ if such a small needle is placed in the center and permitted to deliver 135 mg-hr. of radiation. If the radium could instead be distributed evenly at the periphery of the sphere of 2 cm. diameter, it is evident that the same number of milligram-hours would deliver about 1,000 r_γ to the center. In either case 1,000 r_γ is the minimum dose delivered to any part of a spherical mass. The latter distribution of the radium would give a more homogeneous dose. This distribution can be approached by using a number of small applicators placed symmetrically at the periphery of the mass. From a practical point of view the sources cannot be distributed evenly over the periphery, and somewhat greater variation in dosage therefore has to be expected. Tables have been made to show how many milligram-hours are needed to deliver 1,000 r_γ to any size spherical mass. Such tables which are partly checked by actual experiments show that the "inverse square law" gives values which are accurate enough for masses up to 6 cm. diameter. If the diameter is 1 cm., 34 mg-hr. are needed to deliver 1,000 r_γ and the square of the diameter in centimeters times 34 gives the number

of milligram-hours required to deliver a minimum dose of 1,000 r_γ to any particular sphere. The number of millicuries-destroyed to deliver 1,000 r_γ is equal to 0.25 times the square of the diameter in centimeters. Masses of other shapes may be considered as several spheres.

Radon implants are often used for interstitial irradiation. If gold implants are used with 0.3 mm. thick wall the dose in γ-ray roentgens would be slightly larger than for the 0.5 mm. platinum filtration.

The effect on the tissues depends also upon the time distribution of the radiation; 1,000 r_γ corresponds to a threshold erythema dose when given in a relatively short time. Table VII gives the relation between milligram-hours or millicuries-destroyed and threshold erythema dose. As a matter of fact no considerations of time effect have been used in developing this table. It is a strictly physical equality.

A minimum dose of 7,000 r_γ is often required for treatments of carcinoma. When large tumors are treated, it is necessary to consider the general effects of the radiation, and it is not always possible to give the full dose required in one application. This table is for sources of radiation distributed uniformly throughout the mass.

When radon is used for treatments, the disintegration of this element has to be accurately considered. Table VIII gives the percentage of radon remaining after various time intervals. If the "strength" of a radon container is known at a certain time, its strength at any other time can therefore be calculated by means of these values.

TABLE IX

TIMES REQUIRED TO DELIVER CERTAIN MILLICURIE-HOUR PER INITIAL MILLICURIE

Mc-hr. per Initial mc.	Time			Mc-hr. per Initial mc.	Time	
	Days	Hours	Minutes		Days	Hours
2	0	2	1	52	2	2
4		4	4	54	2	21
6		6	9	56	3	1
8		8	16	58	3	4
10		10	25	60	3	7
12		12	36	62	3	11
14		14	50	64	3	15
16		17	13	66	3	19
18		19	24	68	3	23
20		21	44	70	4	3
22	1	0	6	72	4	7
24	1	2	32	74	4	11
26	1	5	0	76	4	16
28	1	7	30	78	4	21
30	1	10	5	80	5	2
32	1	12	42	82	5	7
34	1	15	14	84	5	12
36	1	18	4	86	5	17
38	1	20	51	88	5	23
40	1	23	42	90	6	5
42	2	2	42	95	6	21
44	2	6	9	100	7	16
46	2	8	4	110	9	17
48	2	11	14	120	12	20
50	2	14	20	130	21	0

The table also gives the number of millicurie-hours of radiation obtained from 1 mc. in a certain length of time.

It is important to know for how long a time a certain amount of radon should be used to deliver an even number of millicurie-hours. Table IX can be used for this purpose. If the number of millicurie-hours desired is divided by the number of millicuries available at the beginning of the treatment, the number of millicurie-hours per initial millicurie which is required is found. By looking up this figure in column one, the corresponding time is found in the next columns. (Interpolate if necessary.)

Further information concerning physical measurements can be found in the radiological journals. The following publications have been used as a basis for this report:

1. Science of Radiology. Edited by Otto Glasser. Charles C Thomas, Springfield, Illinois, 1933.
2. Failla, G. Development of filtered radon implants. Am. J. Roentgenol. & Rad. Therapy, 1926, *16*, 507–525.
3. Recommendations of the International Committee for Radiological Units (Chicago, 1937). *Radiology*, 1937, *29*, 634–636.
4. Laurence, C. G. Radium Dosage. National Research Council of Canada, Bulletin No. 17, 1936.
5. Martin, H. E., Quimby, E. H., and Pack, G. T. Calculations of tissue dosage in radiation therapy. Am. J. Roentgenol. & Rad. Therapy, 1931, *25*, 490–506.
6. Mayneord, W. V. Distribution of radiation around simple radioactive sources. *Brit. J. Radiol.*, 1932, *5*, 677–716.
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8. Paterson, R., and Parker, H. M. Dosage system for interstitial radium therapy. *Brit. J. Radiol.*, 1938, *11*, 252; 313.
9. Quimby, Edith H. Comparison of different metallic filters used in radium therapy. Am. J. Roentgenol. & Rad. Therapy, 1925, *13*, 330–342.
10. Quimby, Edith H. Effect of the size of radium applicators on skin doses. Am. J. Roentgenol. & Rad. Therapy, 1922, *9*, 671–683.
11. Quimby, Edith H. Intensity of radiation in the vicinity of filtered radon implants. *Radiology*, 1928, *10*, 365–376.
12. Quimby, Edith H. Physical factors in interstitial radium therapy. Am. J. Roentgenol. & Rad. Therapy, 1935, *33*, 306–316.
13. Sievert, R. M. Die γ-Strahlungsintensität an der Oberfläche und in der nächsten Umgebung von Radiumnadeln. *Acta radiol.*, 1930, *11*, 249–301.
14. Stenstrom, W. Physical factors in teleradium therapy. Am. J. Roentgenol. & Rad. Therapy, 1935, *33*, 296–301.

Submitted by the Research and Standardization Committee at the Annual Meeting of the American Radium Society at St. Louis, May 15, 1939.

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MINNESOTA RADIOLOGICAL SOCIETY

The Fall Meeting of the Minnesota Radiological Society was held at the Mayo Clinic, Rochester, Minnesota, in the afternoon of December 2, 1939. The following program was given:

Experiences with roentgen pelvimetry. G. A. Good, M.D., and A. B. Hunt, M.D.

The proctosigmoiditis of lymphogranuloma venereum. H. M. Weber, M.D.

Pseudo fractures in diseases affecting the skeletal system. Discussion by J. A. L. McCullough, M.D., and J. D. Camp, M.D.

The evaluation of prostigmine, barium chloride, oxygen and pitressin for the elimination of flatus, in roentgenograms of the abdomen. E. E. Seedorf, M.D.

Primary carcinoma of the lung:
Roentgen diagnosis. J. W. Olds, M.D.
Roentgen treatment. E. H. Little, M.D.
Discussion. E. T. Leddy, M.D.

Intrathoracic tumors, S. W. Harrington, M.D.

A business meeting was held after the program, followed by a dinner at 6.30 P.M. at the Hotel Kahler. The speakers at the dinner were H. M. Worth, M.D., who discussed "Radiology in England" and Shaohsun Wang, M.D., whose topic was "The Practice of Medicine in China."

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CONFERENCE OF MID-WESTERN RADIOLOGISTS

The Fourth Annual Clinical Conference of Mid-Western Radiologists will be held

at the Brown Hotel, Louisville, Kentucky, on February 9 and 10, 1940. In the program emphasis is placed on the clinical aspects of problems of interest to radiologists. Most of the presentations are to be given by physicians active in the practice of clinical medicine. The Kentucky Radiological Society is host to the Conference.

J. C. BELL
General Chairman

CORRECTION

In the article by E. A. Merritt on "Roentgen Therapy of Cancer in the Buccal Cavity and of the Cervix Uteri" in the September, 1939, issue of the JOURNAL, the following corrections should be noted:

The first sentence, page 418, should read "Radium therapy in carcinoma of the cervix uteri is almost universally recognized and accepted."

Under Summary, page 420, the first line of the third paragraph should read "Infection is controlled so that, with 1 per cent bicarbonate soda douches during treatment" . . . .

Vol. 43, No. 1

DEPARTMENT OF TECHNIQUE

Department Editor: Robert B. Taft, M.D., B.S., M.A., 105 Rutledge Ave., Charleston, S. C.

ROENTGEN MEASUREMENT OF THE OBSTETRICAL CONJUGATE OF THE PELVIC INLET

By PAUL C. HODGES, Ph.D., M.D., JANE E. HAMILTON, M.S., *and* JED W. PEARSON, JR., M.D.

From the Division of Roentgenology, and the Department of Obstetrics, University of Chicago
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THE importance of the roentgen measurement of the obstetrical conjugate of the pelvic inlet is now thoroughly established in obstetrics and roentgenology. Most workers use lateral roentgenograms, the methods employed for correcting for triangular distortion falling under three general heads:

1. *Correction by Means of a Sacral or Pubic Marker.* A calibrated metal scale is supported above the film and parallel with it at a level supposed to be identical with the level of the sacral promontory and the pubic symphysis. Some workers place the marker in the gluteal cleft, others place it in front of the pubic symphysis. The scale may be notched or perforated at 1 or 0.5 cm. intervals, in which case no computations are needed, the calipered gross conjugate being laid off directly on the image of the marker which is used as a false centimeter scale. Instead of a calibrated marker one may use a marker with only two points on it, the distance between the two being known. Under these conditions correction of the gross conjugate is accomplished by multiplying it with a factor F obtained from the equation

$$F=\frac{M}{y}$$

where

M = the actual distance between the points on the marker

y = the distance between the image of these points as seen in the film.

2. *Correction by Means of Sacral or Pubic Measurement.* When target-film distance (D) and table-top-film distance (e) are fixed and known and the distance from the middle of the sacrum or the pubic symphysis to the top of the table (h) can be measured, no marker is needed, the correction factor being obtained from a graph of the equation $F=\frac{D-(h+e)}{D}$. It is possible to build roentgen apparatus in which D and e are fixed and known; h, however must be measured for each patient, and in our opinion if this measurement is to be significant it must be made by the roentgenologist himself at the time the film is exposed.

3. *Correction by Means of Parallax.* When suitable apparatus is available, accurate measurements of the obstetrical conjugate may be obtained by stereoscopic triangulation, the degree of accuracy depending almost solely upon the precision of the apparatus and the technique of the person who works up the films. We prefer to work up such films by direct measurement of parallax[1] but one may use instead a stereoroentgenometer or a measuring stereoscope. The parallax methods are particularly adaptable to institutions where the volume of work is large and the actual film making is done by technicians. They have the disadvantages of requiring two films rather than one and of requiring considerable time

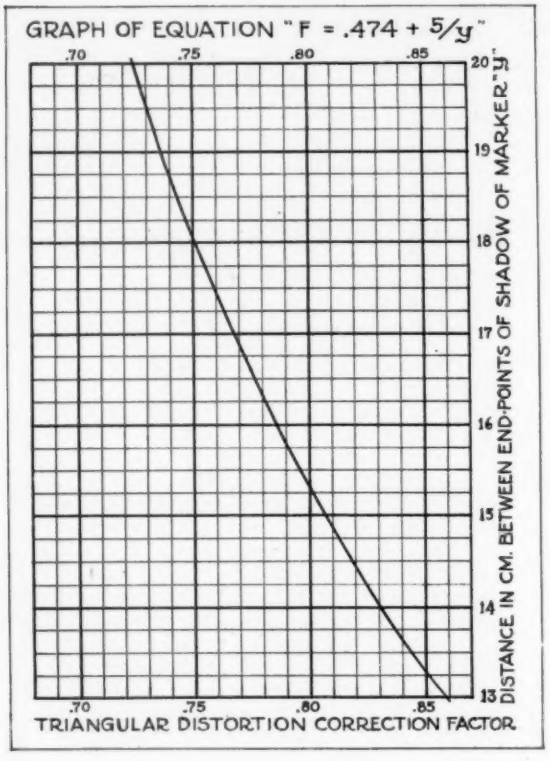

FIG. 1. Graph for obtaining triangular distortion correction factor from surface marker for correction of obstetrical conjugate as seen in lateral pelvic roentgenograms.

for the working up of the films after they have been made.

CORRECTION BY A SURFACE MARKER

The present paper deals with a one-film method for the measurement of the obstetrical conjugate, in which accuracy depends largely upon the precision of the apparatus. The technician must see to it that the patient is in the true lateral position and must bring the arm of a special marker down until it presses firmly against the skin over the uppermost great trochanter, but in our opinion capable technicians can be depended upon for these details. There are no measurements for the technician to make. The method assumes that the conjugate lies halfway between the two great trochanters but the validity of the measurement is affected surprisingly little by pelvic asymmetry even of considerable degree.

The marker is an aluminum arm carrying two perforated lead discs, the perforations being 10 cm. apart. This arm can be moved up or down along a rod that rises perpendicular to the plane of the table top. The perpendicular rod may be supported by a weighted base resting on the table top or it may be attached to a fitting that slides along a rail for the attachment of other accessories. The subject is placed in the lateral position on the roentgen table, her legs flexed on the thighs, her thighs extended on the pelvis as far as comfort will permit. This position increases the lordosis of the spine, brings the anteroposterior diameter of the pelvic inlet more nearly parallel with the long axis of the film and prevents the shadows of the thighs from obscuring those of the pelvis. Either lateral view is satisfactory but with our own apparatus it is more convenient to have the patient lying left side down and the following description refers to the left lateral position.

A single 10″×12″ film is lined up so that its center lies approximately on an imaginary perpendicular axis passing from the target of the roentgen tube down through a point midway between the perforations on the marker and a point midway between the sacral promontory and the pubic symphysis. Accuracy in this alignment of tube, marker, subject and sacrum facilitates identification of the end-points of the conjugate but does not otherwise affect the accuracy of the measurement. As long as these end-points and the perforations in the marker can be seen the film is suitable for measurement.

The general equation for the correction factor is

$$F=\frac{D-e}{2D}+\frac{M}{2y}$$

where

F = correction factor for obtaining net or true conjugate from the gross or distorted conjugate measured on the film

D = target-film distance (in our apparatus 88.5 cm.)

DERIVATION OF EQUATION

Equation	Explanation
1. $\frac{a}{D-h}=\frac{I}{D}$	Triangular proportion based on Figure 2.
2. $a=I\left(\frac{D-h}{D}\right)$	No. 1 simplified.
3. $a=IF$	From No. 2 $\frac{D-h}{D}$ is a factor F which multiplied by the image of the conjugate I yields the true diameter of the conjugate a.
4. $\frac{f}{g}=n \quad f=ng$	In most cases $n=1$ but the method is correct within experimental limits over a considerable range of values of n.
5. $d=h+f$	See Figure 2.
6. $d=h+ng$	Substituting in No. 5 the value of f from No. 4.
7. $g=h-e$	See Figure 2.
8. $d=h+nh-ne$	Substituting in No. 6 the value of g from No. 7.
9. $h=\frac{d+ne}{n+1}$	No. 8 simplified.
10. $h=\frac{d+e}{2}$	In symmetrical pelves where $n=1$.
11. $\frac{M}{D-d}=\frac{y}{D}$	Triangular proportion based on Figure 2.
12. $d=\frac{D(y-M)}{y}$	No. 11 simplified.
13. $F=\frac{D-h}{D}$	From Equation No. 3.
14. $F=\frac{D-\left(\frac{d+e}{2}\right)}{D}$	Substituting in No. 13 the value of h from No. 10.
15. $F=\frac{D-\left[\frac{\frac{D(y-M)}{y}+e}{2}\right]}{D}$	Substituting in No. 14 the value of D from No. 12.
16. $F=\frac{D-e}{2D}+\frac{M}{2y}$	No. 15 simplified.
17. $F=.474+\frac{5}{y}$	Substituting in No. 16 the values for D, e and M in our particular apparatus.

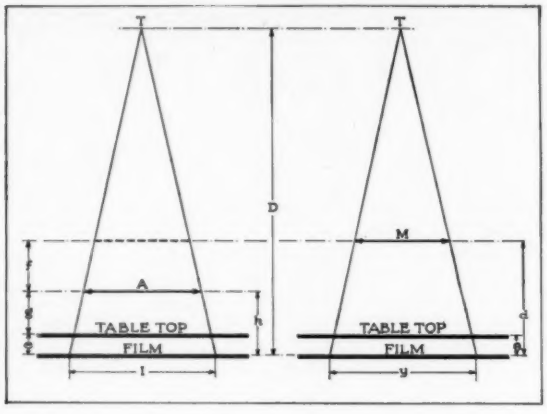

FIG. 2. D, target-film distance; e, table-top-film distance; A, actual distance between sacral promontory and pubic symphysis (obstetrical conjugate); I, gross or distorted image of obstetrical conjugate as seen in roentgenograms; h, height of sacrum and pubic symphysis above plane of film; f, distance from sacral promontory and pubic symphysis to skin above right great trochanter (patient lying in left lateral position); g, distance from sacral promontory and pubic symphysis to skin above left great trochanter; M, distance between the points on a surface marker placed in contact with the skin over the right great trochanter and arranged parallel with the plane of the film; y, distance between points on the distorted image of the marker as seen in the roentgenogram; d, the height of the marker above the film; D, e and M are fixed and known. I and y can be measured on the film.

e = distance between the upper surface of the table top and the plane of the film (in our apparatus 4.6 cm.)

M = actual distance between the points on the marker (in our apparatus 10 cm.)

y = gross distance between the shadows of these points as seen in the film

Substituting these values, the equation for our own particular apparatus becomes $F = 0.474 + 5/y$. For convenient application this equation is expressed as a graph (Fig. 1).

This method is the direct outgrowth of a procedure developed by us for the measurement of occipitofrontal diameter in fetal skulls. We have published skull measurements obtained in this manner[2] but have not heretofore described the method of making the measurements.

EXPERIMENTS

Ten subjects were examined, three films being made in each case—a stereoscopic pair for parallax and one with the tube directly above the center of the film for the position methods. In 9 of the cases computations were made by parallax, by means of the sacral marker, by sacral measurement and by means of the surface marker.

TABLE I

Case No.	Parallax used as Standard	Obstetrical Conjugate in Centimeters Measured by					
		Sacral Marker	Error	Sacral Measurement	Error	Surface Marker	Error
1	12.1					11.9	−.2
2	12.1	12.7	+.6	12.3	+.2	12.2	+.1
3	11.4	11.8	+.4	11.4	.0	11.5	+.1
4	10.9	11.3	+.4	11.2	+.3	10.9	.0
5	9.9	10.2	+.3	10.0	+.1	9.8	−.1
6	11.3	11.5	+.2	11.1	−.2	11.3	.0
7	13.9	13.8	−.1	14.3	+.4	13.6	−.3
8	11.5	11.8	+.3	11.5	.0	11.5	.0
9	12.3	12.6	+.3	12.4	+.1	12.2	−.1
10	12.3	12.8	+.5	12.3	.0	12.1	−.2
Average			+.3		+.1		−.07

In one case, only parallax and sacral marker measurements were obtained. Assuming, for the sake of argument, that the parallax measurements are an accurate indication of the actual measurement of the obstetrical conjugate, it was found that with the surface marker there was a mean error of −0.7 mm., with the sacral measurement a mean error of +1 mm., with the sacral marker a mean error of +3 mm. The details are given in Table 1.

CONCLUSIONS

1. There is presented an objective method for the measurement of the obstetrical conjugate of the pelvic inlet by means of a single lateral pelvic roentgenogram.

2. The only special apparatus needed is a 10 cm. scale that rests on the uppermost great trochanter supported so that it lies parallel with the plane of the film.

3. Net or true obstetrical conjugate is computed by measuring the conjugate as it appears on the film and multiplying this gross value by a factor F obtained from the equation

$$F=\frac{D-e}{2D}+\frac{M}{2y}$$

where

F = correction factor
D = target-film distance
e = table-top-film distance
M = diameter of the surface marker
y = diameter of the roentgen image of the surface marker.

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2. Hodges, P. C., and Hamilton, J. E. Pelvic roentgenography in pregnancy. *Radiology*, 1938, *30*, 157–166.

A SIMPLE TECHNIQUE AND NEW INSTRUMENT FOR RAPID ROENTGEN PELVIMETRY*

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I. INTRODUCTION

As roentgen pelvimetry becomes more generally used, there is increasing need for a simple, coherent technique. At present there is an understandable skepticism about pelvimetry on the part of some obstetricians who have delivered babies *per vaginam* after a roentgenologist has given the opinion that they could not be so delivered. Obviously they could, and were. But should they have been? Many a family may be bearing the stigma of mental insufficiency in a child through no fault of its genes, but because of cerebral trauma at birth. In considering this problem, due recognition is given the fact that soft tissue architecture and pelvic dynamics are factors in its solution.

The requirements for a reliable system of pelvimetry, which this paper is designed to construct, are these:

1. Simplicity. The method demands nothing beyond ordinary roentgen-ray facilities, not even stereoscopy. Two roentgen exposures of the pelvis, a centimeter rule, and a chart or instrument for distortion correcting are all that is necessary. Reading the directions is, naturally, far more time consuming than actually making the computations.

2. Intelligibility. These measurements are not to be made by engineers, but by obstetricians and roentgenologists. The fundamental concepts are certainly comprehensible to any physician who is willing to read the explanation.

3. The accuracy of the measurements can usually be considered not more than 0.5 cm. out of the way.

4. The reports are in linear distances, the same as those with which the obstetrician has been familiar for years. The following measurements are computed:

Pelvic Inlet:

1. True conjugate or anteroposterior diameter.
2. Widest transverse diameter.

Mid-pelvis:

1. Bisischial, or transverse diameter at ischial spines.
2. Anteroposterior diameter from hollow of sacrum to a line even with the symphysis.

Pelvic Outlet:

1. Tuberischial, transverse diameter.
2. Posterior sagittal, anteroposterior from lower sacrum to middle of tuberischial line.

Fetus:

1. Circumference of skull, from which can be recognized the size of the fetus as well as its age in weeks.

The method to be presented requires not more than a few minutes for completing an entire set of measurements and calculations. It is amply accurate for clinical use.

II. FUNDAMENTAL CONCEPTS

A man's shadow, as he walks along the street, may measure several feet larger than he, and the roentgen shadow of a pelvic bone, likewise, is somewhat larger than the bone itself.

How much larger is a given true conjugate on the film, over the real, anatomic distance? It is self evident that if the roentgen tube is kept at the same distance (and it always must be at just 30 inches from the film with the method to be described), the disproportion between real size and size on the film will depend on the distance of the pelvis from the film. The closer the pelvis approaches to the film, the less will be the exaggeration of its size. Mathematically speaking, with similar

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triangles the bases are proportional to the altitudes, or:

$$\frac{\text{tube-film distance}}{\text{tube-film distance minus object-film distance}} = \frac{\text{image diameter}}{\text{object diameter}}$$

The problem, then, is: How far was the pelvis, or that portion of it under consideration, from the film when the roentgenogram was taken? Assume it is the true conjugate we are measuring, and we are looking, therefore, at the lateral view. The patient was lying on her right side when this exposure was made: that is, the true conjugate was separated from the table by the distance from the trochanter (on which she was lying) to the symphysis. But what is this distance between trochanter and symphysis? That can be directly measured on the other film, which was taken as an anteroposterior view.

The acquired data now are:

(a) Measured distance between promontory and symphysis—on the lateral view.

(b) Distance of this diameter (true conjugate) from the film—on the anteroposterior view.

Simple geometry as was stated yields, finally, the desired measurement: the true, anatomical diameter.

In brief, we measure a diameter on one film and determine from the other film just how far from the table that diameter lay. With these two measurements and the known tube-film distance, we can solve for the anatomical distance.

The second measurement (the object-film distance) is called the "correction factor." The interposition of the soft tissues between the bony parts and the table has been taken into account in arriving at an accurate correction factor. It will be quickly recognized, furthermore, that the correction factor is not critical—a difference of centimeters in the correction factor represents a difference in the final answer of only millimeters.

III. EQUIPMENT

The Slide-Rule. In the familiar proportion formula, we could substitute the three known quantities and solve for the anatomic distance. But this would be a tiresome procedure, and one subject to arithmetic errors. There are available several short-cut methods for computing this equation. Since these methods were not as rapid and as simple as could be desired, we fashioned a simplified slide-rule, designed especially for this system of pelvimetry. Its use is self explanatory and very easy (see Fig. 3).

If the slide-rule is not used: Since the film, when exposed through a Potter-Bucky diaphragm, is 5 cm. below the table top, this 5 cm. must be added to the "correction factor" (the object-film distance). The roentgenogram, after all, shows object-to-table-top distance; but we must know object-to-film distance. (This 5 cm. is neglected when using the slide-rule, since it was added in the design of the instrument.)

The Twirled Adhesive. Measuring the circumference of the fetal skull, as described later, presented mechanical difficulties. We have found it convenient to use the following: A 50 cm. length of ordinary adhesive tape, 1 cm. wide, is rolled with its gummed side out—making a long, thin tube with considerable "stickiness." This can be placed along the skull edge, with the film on the shadow-box, and a crease made to designate the length of the circumference. The adhesive tape is then measured on any centimeter scale.

Crayon. It is advantageous to mark significant points before measuring. "China-marking" and "eyebrow" pencils are very good. These marks can later be erased without damage to the film.

The Films. The two films consist of a lateral and an anteroposterior view of the pelvis. They must include symphysis, sacrum, tuberosities and trochanters. They

are taken with the target just 30 inches (76 cm.) from the film, using a Potter-Bucky diaphragm. Two hundred cubic centimeters of air in the bladder help in locating the posterior margin of the symphysis (and incidentally, this provides contrast for soft tissue observations). In the anteroposterior view, the feet should be together, with the toes pointing up. For the lateral view, it is best to center over the hips.

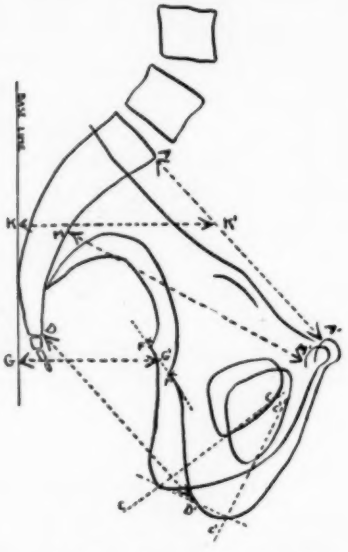

FIG. 1. Lateral view of pelvis for locating measurements described in text. AA¹, anteroposterior diameter of pelvic inlet; cc and c¹c¹, guide lines for locating tuberischial points; DD¹, posterior sagittal diameter of pelvic outlet; FF¹, location of spines on lateral view of pelvis; GG¹, distance from midway between spines FF¹ to table top; KK¹, measurement for distance of transverse diameter of inlet to table top; MM¹, anteroposterior diameter of mid-pelvis.

IV. TECHNIQUE OF MEASUREMENTS

The routine for obtaining the usual measurements is described below in the sequence which has been found most practical. Secure the "measured distance" and the "correction factor." If the slide-rule is to be used, set the arrow of the slide under the proper "correction factor," and set the movable hair-line over the proper "measured diameter." Read off the anatomic or real diameter on the "corrected diameter" scale.

1. *True Conjugate*

(Anteroposterior Diameter of Inlet)

On the lateral view: Measure the shortest distance between the anterior margin of the sacral promontory and the posterior margin of the symphysis. This is the "measured diameter" (Fig. 1, AA¹).

To correct for distortion: On the anteroposterior view measure the distance between the greater trochanter limits, divide by 2 and subtract 3 (Fig. 2, BB¹). We divide by 2 to obtain the distance from symphysis to greater trochanter. We subtract 3 cm. because experience has shown that it is enlarged to this extent on the film, as compared to measurement on the patient.

This number is now called the "correction factor."

2. *Anteroposterior Diameter of Mid-pelvis*

On the lateral view: Draw a line along the posterior wall of the symphysis, continuing toward the obturator foramina. Draw a perpendicular to this line, from midway between the tip of the promontory and the sacrococcygeal joint. This is the "measured diameter" (see Fig. 1, MM¹).

To correct for distortion: Correction factor for this is the same as for the other anteroposterior diameters in the midline; that is, the same as for the true conjugate.

3. *Posterior Sagittal*

On the lateral view: Draw a line backwards along the lower border of each obturator foramen (see Fig. 1, cc and c¹c¹). Where these lines pass through the posterior edges of the ischial rami, place marks. These points are taken as the ischial tuberosities. Mark the midpoint between them. Measure from this midpoint to the tip of the sacrum (see Fig. 1, DD¹). This is the "measured diameter."

To correct for distortion: Since this diameter lies in the same plane as the true conjugate, the same "correction factor" is used as was used for the true conjugate.

4. *Between the Ischial Spines*

On the anteroposterior view: Measure the distance between the spines (Fig. 2, EE^1). This is the "measured diameter."

To correct for distortion: On the lateral view, mark the two spines and the midpoint between them (Fig. 1, FF^1). Measure the shortest distance (Fig. 1, GG^1) from this point to the sacrum *base line.* The latter is a line drawn parallel to the film edge, touching the posterior border of the sacrum.

To correct the correction factor for distortion: (In the same way that we correct the original diameter, we can modify the correction factor when it is too much enlarged. This improves the final accuracy.) Since the above diameter (midpoint between spines to base line) is in the midplane of the pelvis, it may be corrected by the same factor as was used to correct the true conjugate. Using, therefore, the above diameter (midpoint between spines to baseline) as "measured distance," and using the correction factor for the true conjugate as "correction factor," derive the "corrected length." This measurement (the corrected length) is the "correction factor" for the bisischial diameter.

5. *Transverse of the Outlet*

On the anteroposterior view: Starting at the brim of the pelvis, and running downward longitudinally through the outer border of each obturator foramen, there is a pronounced linear density, which appears as a heavy white line representing the lateral pelvic wall. With the crayon, extend these lines caudally, continuing their natural directions. Where the crayon lines pass through the caudal edges of the ischial rami, place marks (Fig. 2, HH^1). These points are taken as the ischial tuberosities. Measure the distance between them. This is the "measured diameter."

To correct for distortion: Since the transverse of the outlet and bisischial diameters lie close together, use the same "correction factor" as was finally used for the bisischial.

6. *Transverse of the Inlet*

On the anteroposterior view: Measure the widest transverse diameter of the pelvic brim. This is the "measured diameter" (Fig. 2, JJ^1).

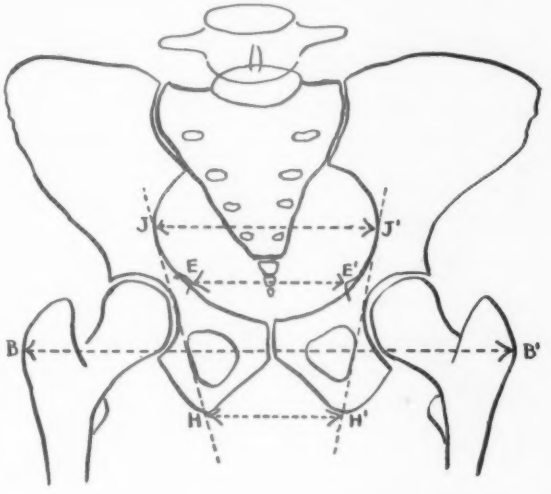

FIG. 2. Anteroposterior view of pelvis for locating measurements described in text. BB^1, diameter between greater tuberosities; EE^1, transverse diameter of mid-pelvis at spines; JH and J^{1}H^1, guide lines for locating the tuberischial points; HH^1, transverse diameter of pelvic outlet at tuberischial points; JJ^1, widest transverse diameter of pelvic inlet.

To correct for distortion: On the lateral view, draw a line from the promontory to the top of the symphysis. Mark the junction of the posterior and middle thirds of this line. Measure the shortest distance from this point to the *base line* used in correcting the bisischial diameter (Fig. 1, KK^1). Subtract 2 cm. (because the true transverse plane lies below the anteroposterior plane of the inlet).

To correct correction factor for distortion: Since the above diameter (junction of posterior and middle thirds to base line) is in the midplane of the pelvis, it may be corrected by the same factor as was used for correcting the true conjugate. Using the above diameter (junction of posterior and middle thirds to base line minus 2) as "measured distance" and using the correction factor for the true conjugate as "cor-

rection factor," derive the "corrected length." This measurement (the corrected length) is the "correction factor" for the transverse of the inlet.

7. *Circumference of Fetal Skull*

Step A. On the anteroposterior view: Measure the circumference of the skull using the twirled adhesive. This is the "measured perimeter."

To correct for distortion: On the lateral view, measure the shortest distance from the approximate center of the skull to the same *base line* as was used for correcting the bisischial diameter.

To correct correction factor for distortion: Since the approximate center of the skull lies near the midplane of the pelvis, the same correction factor is used as was used for the true conjugate. Using the above diameter (center of skull to base line) as "measured distance" and using the correction factor for the true conjugate as "correction factor," derive the "corrected length." This measurement (the corrected length) is the "correction factor" for the skull circumference in the anteroposterior view.

Step B. On the lateral view: Measure the circumference of the skull, using the twirled adhesive. This is the "measured perimeter."

To correct for distortion: On the anteroposterior view, measure the shortest distance from the outer border of a trochanter to a line drawn through the approximate center of the skull and parallel with the long axis of the body. (Measure from the trochanter on which the patient was lying in the lateral view.) Subtract 3 cm. This is the "correction factor."

Step C. On the side of the slide-rule bearing red numerals, derive the "corrected perimeters" for Steps A and B, and average the two. This is a theoretical skull circumference, but conforms roughly to that measured post partum in the biparietal plane. Skin thickness is calculated into the slide-rule, so that the "corrected perimeter" scale reads skull circumference including skin.

(It is assumed that the fetal head did not move appreciably in relation to the pelvis between the taking of the anteroposterior and lateral roentgen exposures.)

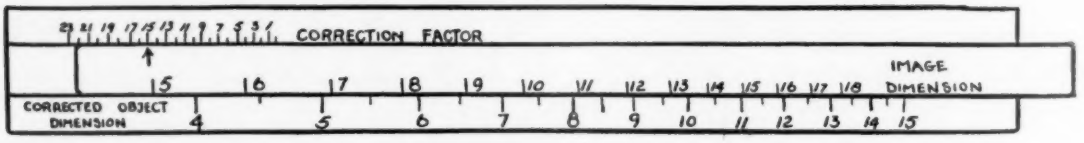

FIG. 3. Slide-rule, one face.

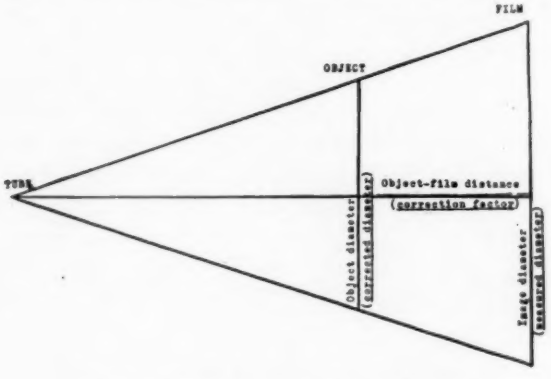

FIG. 4. Enlargement of the roentgen shadow.

8. *Age of Fetus*

Place the movable hair-line over the determined skull circumference on the "corrected perimeter" scale. Read approximate fetal age on the lowermost scale.

V. COMMENTS

A routine has been presented for roentgen pelvimetry. It is designed for quick clinical use in obstetrics. It is based on simple geometry, and introduces a new

instrument, with a much simplified technique. The instrument is a slide-rule constructed specially for this system of pelvimetry.

The method described has been evolved over the last several years in clinical use at two busy hospitals, where well over 500 cases were examined. In many instances, the true conjugate was checked against Thom's methods (a) in which the film is viewed as if by the target of the roentgen tube, and a plate of glass is placed in the plane of the patient's inlet, (b) in which a notched brass centimeter rule is fastened to the midline of the patient when the lateral roentgen exposure is made. The results were satisfactorily alike, while our measurements were more quickly and more easily obtained. The Ball pelvicephalometer was used in a series of cases, but difficulty was encountered in following the curved lines on the chart. A more serious objection to the Ball technique, however, is this: that volumetric measurements are computed. Not only have these proved unreliable as indices of disproportion, but linear measurements would seem to be preferable for the obstetrician. These he understands, and his clinical examination can be easily compared with the roentgen report. Although it is rather difficult to measure a pelvis during cesarean section, we had this done on two occasions and were satisfied with the correlation. We have checked each of the measurements repeatedly on the dry skeleton, by taking roentgenograms with varying shifts of the tube. There is a liberal margin of safety in the placement of the pelvis, but it is important to obtain a fairly true lateral view. Despite our careful checking, we are aware that the highest degree of accuracy is not yet established, and for this reason we contemplate (and recommend to others who are interested) making roentgen examinations of cadavers for correlation with the true, anatomical measurements.

It is our hope that the simplicity and completeness of the method described will invite more clinicians and roentgenologists into the field of roentgen pelvimetry for guidance in their obstetrical problems. We feel that accurate and simple roentgen pelvimetry is a forward move towards reducing the number of cases which will be subjected to an unsuccessful or undesirable trial of labor. For it is our suspicion that mental disease statistics may someday show that every labor which concludes with a living baby is not necessarily, from all aspects, a "successful" one.

THE BOOK-SHELF STEREOSCOPE

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LOS ANGELES, CALIFORNIA

IN ORDER to obtain the best view of a completed roentgenogram it is necessary to place the film before a properly illuminated box. It has been shown that various densities in the film can best be studied with a varying degree of light intensity. The illumination at the surface of the box should be approximately 2000 meter candles (200 foot-candles).[1] The light which emanates from the viewing box should be bluish-white in color. Single chest films are most frequently used in general work because of the lack of stereoscopic units and also for reasons of economy.

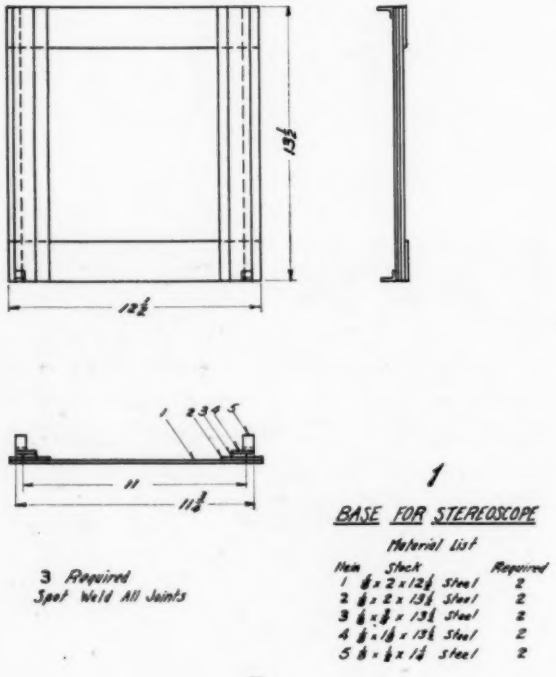

FIG. 1

In many offices it is not always possible to find suitable space for a full-sized stereoscopic unit. In order to conserve space it occurred to me that I might build a stereoscopic unit into a bookcase so that the illuminator could be used either as single light source and by adding platforms with tracks the entire base of the bookcase could be made available for the apparatus. The drawings (Figs. 1, 2 and 3) show the plans and the type of material used.

The complete unit consisting of two illuminators and mirror can be arranged to fit into the 5-foot book-shelf of usual depth of 14 inches. The height of the second shelf should be 18 inches and should be set back 6½ inches to accommodate the illuminators when in the closed position.

The three units are mounted to the lower shelf, as shown in Figure 4, by mounting bases (Fig. 1) screwed to the shelf. The sliders (Fig. 2) fit into these bases and are provided with suitable stops to prevent being pulled out too far. The illuminators are mounted on the slider by a special base and support (Fig. 3 *B* and *C*). This base

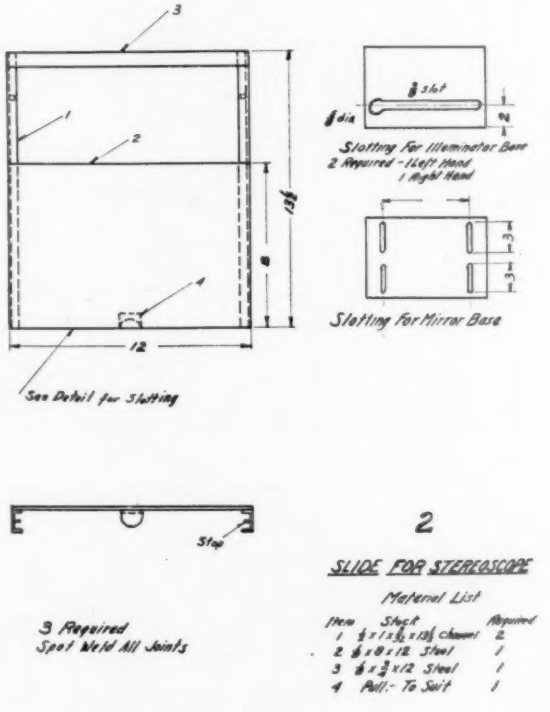

FIG. 2

[1] Weyl, C., and Warren, S. R., Jr. Apparatus and Technique for Roentgenography of the Chest. Charles C Thomas, Springfield, Ill., 1935, p. 54.

is made so that the illuminators can be entirely removed. The mirror mount requires an additional slide (Fig. 3 *A*) to bring the center line of the mirror in center line with the illuminator or film. This mirror mount can be made to suit other types of mirrors.

Operation. From closed position (Fig. 4) the slides are pulled out to maximum position. The illuminators are turned on their base to bring glass toward the mirror (Fig. 5). The mirror is placed on its slide and further pulled out and aligned with the illuminators.

The advantages of the book-shelf stereoscope are that it is simple in construction; it takes up very little space; and it is economical.

I wish to take this opportunity to thank Mr. K. F. Burkholder of the Westinghouse X-ray Company for many helpful suggestions in the development of the apparatus.

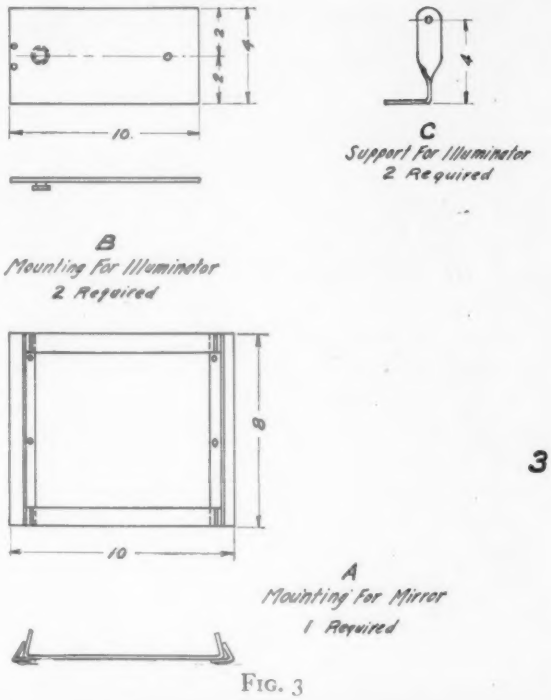

FIG. 3

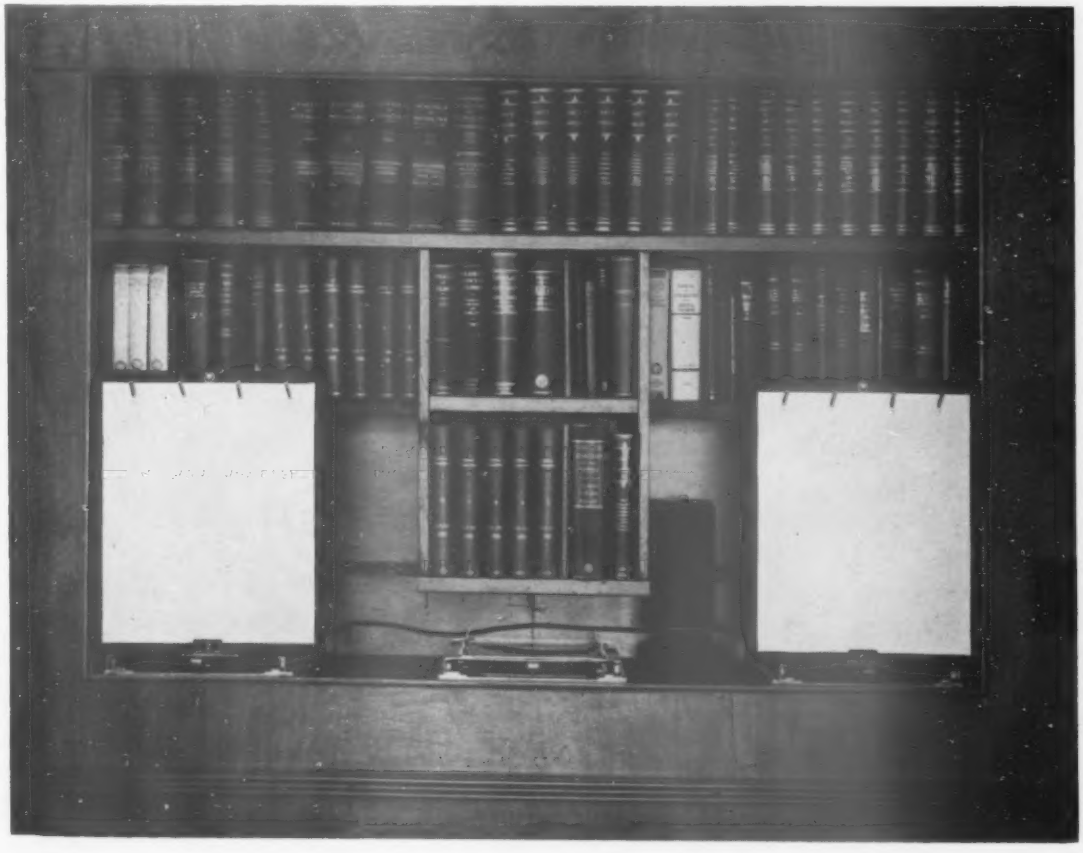

FIG. 4. Note the removable mirror behind the illuminating box on the right. The extension platforms are all telescoped in the base of the bookcase.

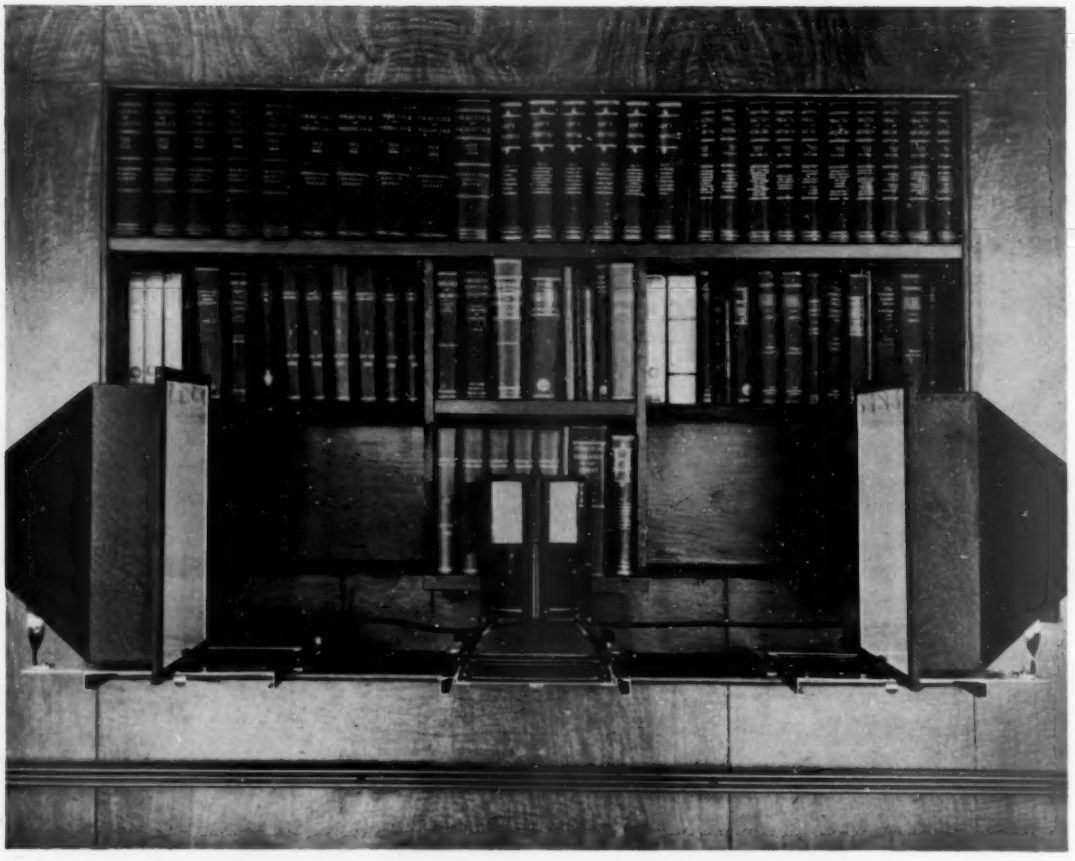

FIG. 5. Three platforms pulled out from the case. On the central platform note the mirror for stereoscopic use.

Vol. 43, No. 1

THE FLUOROENTGENOGRAPH

By FRANZ J. LUST, M.D.
NEW YORK CITY

THE importance of fluoroscopy in the examination of the gastrointestinal tract is well recognized. The routine procedure of first fluoroscoping and then taking roentgenograms in different positions does not always satisfy. It often happens that certain types of movements of the stomach, duodenum or appendix are only seen during fluoroscopy. These conditions, partly physiological, partly pathological, cannot always be visualized by roentgenograms which are taken *after* fluoroscopy. Even if the fluoroscopy is interrupted to take a roentgenogram a certain time must elapse until all the switches are set and an exposure can be made. For many years certain devices have been on the market to improve our roentgenological work. I have only to mention those constructed by Baensch, Berg, Chaoul and others. Most of these appliances, however, work only in one position and most of them are constructed for exposures with the patient in the upright position.

For many years we have been working with these cassettes, the most popular of which is the one constructed by Berg. With this outfit four exposures are made on one film of the 18 by 24 cm. size. After two exposures are made, the cassette has to be taken out of the frame and put back after being turned upside down. As this has to be done while the fluoroscopic room is dark the procedure is a rather difficult one. Another feature is that the Berg frame cannot be used easily in the horizontal position. Some of the other attachments are expensive, clumsy or difficult to handle.

In 1936 we therefore designed an attachment to overcome some of the difficulties of the former constructions. Our device, the fluororoentgenograph, is constructed as follows: there is a lead plate with an opening to the right of the middle. Toward the patient there is a round, semispherical part which serves for compression, toward the examining physician a small fluoroscopic screen covers the opening of the lead plate. To the left of the fluoroscopic screen there is a cassette holder which during fluoroscopy is entirely protected by the lead plate. A cassette 8×10 inches in size is placed in the holder. The cassette holder with the cassette can very easily be moved to the right between the opening

FIG. 1

in the lead plate and the fluoroscopic screen as the holder runs on a rail. We are therefore able to switch the cassette in its place in upright and in horizontal position. For the first exposure (right lower quadrant of the film), the holder with the cassette is arrested at the end of the fluoroscopic screen by a button which being pushed releases the cassette so that the holder can be moved far to the right side and the second exposure (left lower quadrant of the film), can be made. A special device permits the

rotation of the cassette in the cassette holder so that the other side of the film can now be exposed in the same way. The entire fluororoentgenograph can be fixed on a stand (see Fig. 1) or exchanged with the normal fluoroscopic screen. There are special screws to move the fluororoentgenograph upwards and downwards, so that it can be fixed at any angle as needed for special work.

The advantages of our fluororoentgenograph are the following:

(1) Cassettes of routine size (8×10 inches) are used.
(2) There are four exposures on one film. Only one procedure is necessary for filling and developing.
(3) The fluororoentgenograph can be used with any roentgenological outfit, in any position (horizontal and vertical).
(4) The simplicity of construction enables easy, undisturbed work.
(5) During the exposure we see on the fluoroscopic screen the part we are later to see on the film.
(6) The rotating of the cassette is done *inside* the fluororoentgenograph. The cassette need not be removed.
(7) The fluororoentgenograph can be manufactured easily by any skilled mechanic.

The fluororoentgenograph is especially useful for work in gastroenterology. Films taken during filling of the stomach, of the movement of the cardiac portion of the esophagus and stomach, the question of motility and peristalsis of stomach, pylorus and duodenum are fields in which this attachment will be most widely used. The duodenal cap in its different positions is especially easy to study. Films in the left oblique position to reveal changes in the anterior and posterior wall of the duodenum are easily taken. Until now it has often been difficult to visualize these parts as the stomach overlapped the cap in the left oblique position. The second part of the duodenum and the question of duodenitis can easily be studied. The same is true for the small intestine, appendix, colon and gallbladder. In our work on the mucosa of the colon we have already obtained good results with our technique.

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ABSTRACTS OF ROENTGEN AND RADIUM LITERATURE

ROENTGEN DIAGNOSIS

SKELETAL SYSTEM

Kramer, Benjamin, and Halpert, Béla. Marble bones. 1. Clinicopathologic observations. *Am. J. Dis. Child.*, April, 1939, *57*, 795–808.

The authors report a case of the typical form of marble bones (osteosclerosis fragilitas generalisata, Laurell and Wallgren; Marmorknochenkrankheit, Albers-Schönberg; osteopetrosis, Karshner), with clinical, pathologic, roentgenologic and chemical data. Their case, as far as they could ascertain, was identical with a considerable number of those reported as to approximate age of the patient, the roentgenographic appearance of the skeleton and the clinical course of the disease, with blindness and fatal termination.

The post-mortem observations in their case suggest that the changes in the skeleton about the centers of ossification and the resulting production of a faulty osseous structure were the principal lesions. The changes in the bone marrow were slight and secondary, so that the scattered blood-forming islands in the liver, spleen, kidneys and lymph nodes were perhaps remains from fetal life rather than part of a compensatory mechanism. Of the organs of internal secretion, the thymus, the thyroid, the parathyroid and the adrenal glands presented nothing unusual, nor could any morphologic changes be detected in the hypophysis cerebri.

Evidences of avitaminosis were present. The patient, three and one-half months of age, presented a degree of rickets which they had never seen in one so young. The rachitic changes were very resistant to therapy. They also felt there was some evidence of possible faulty utilization by the patient of the antiscorbutic factor. They do not infer that marble bones is itself a type of avitaminosis. The metabolic defect, whatever it is, confers on the patient susceptibility to certain avitaminosis, the manifestations of

which are modified by the lesion characteristic of marble bones, which not only produces morphologic changes but confers a state of refractoriness to appropriate therapy.

According to Schmidt it is desirable to separate the cases in which marble bones occur in infancy or in early childhood from those in which the condition appears later in life. He contends that in the adult type of the disease usually the changes in the blood-forming organs and the blood (osteosclerotic anemia) dominate the picture, while in the childhood type the skeletal changes are paramount. Indeed, in the latter type the changes in the osseous system are so progressive and severe that the afflicted children usually do not survive to reach complete skeletal development.—*R. S. Bromer.*

KRAMER, BENJAMIN, YUSKA, HENRY, and STEINER, MATTHEW M. Marble bones. II. Chemical analysis of bone. *Am. J. Dis. Child.*, May, 1939, *57*, 1044–1057.

The term "marble bones" refers to certain gross physical characteristics of the bone in osteopetrosis rather than to its actual chemical composition or to the crystal structure of its organic matter. Although several post-mortem examinations have been made in cases of this condition, few complete reports on the chemical composition of the bones are available. The authors' objective in their study was (1) to determine the chemical composition of the inorganic material (a factual aim); (2) to provide, if possible, an explanation for the peculiar properties of this bony material, such as its roentgen and histologic appearance and its brittleness, and (3) to elucidate the mechanism of the disease.

They report the summary and conclusions of their study of a case of osteopetrosis as follows:

"The percentage of ash, of calcium and of phosphorus in the bones of an infant with osteopetrosis, where the characteristic lesion was present, was distinctly higher than in the corresponding bones of a normal newly born infant, except in the flat bones of the skull.

"The ratio of residual calcium to phosphorus was in harmony with the idea that the calcium-phosphorus compound in marble bones is tertiary calcium phosphate.

"In analyses of the upper and lower tibial epiphyses, evidence of a calcium-phosphorus compound having a lower ratio of calcium to phosphorus was obtained.

"When calculated in terms of acid-base equivalents, the total fixed base content as determined by electrodialysis exceeded the sum of the calcium and the magnesium content by 1.2 to 5.9 per cent. Part of this excess of base undoubtedly was represented by the sodium and potassium content of the bone. There is therefore no major basic component in marble bones which is not represented by the well known elements of calcium, magnesium, sodium and potassium.

"The value of n, i.e., the molecular ratio of calcium phosphate to calcium carbonate in the bones of the infant with osteopetrosis, was found to be approximately 2, corresponding to that found in normal adult bone or in the bones of rachitic infants, i.e., has more carbonate than bones of normal infants of the same age.

"There was a satisfactory agreement between the ash content as determined by heating dried fat-free bone at 500 C. and the ash content calculated on the assumption that calcium and magnesium exist as carbonates and that phosphorus is present as tertiary calcium phosphate. On the same assumption, determination of the acid-base balance showed a slightly positive base balance.

"The significant findings therefore are a higher carbonate content and hypermineralization. A high carbonate content is also present in adult and rachitic bone and may account for the increased fragility. Hypermineralization is a finding inconsistent with the diagnosis of rickets. It is therefore likely that the combination of high carbonate content and hypermineralization characterizes the mineral content of marble bones."—*R. S. Bromer.*

ATSATT, RODNEY F. Acute osteomyelitis of a vertebral body following compression fracture. *J. Bone & Joint Surg.*, April, 1939, *21*, 346–352.

Atsatt reports a case of compression fracture of the body of the second lumbar vertebra. On this primary lesion was superimposed a secondary hematogenous infection which was localized within the fractured vertebral body. He believes that this is the first case to be reported of an acute osteomyelitis developing at the site of a recent compression fracture.

The hematogenous infection was caused by a streptococcus, possibly metastatic from a gingivitis. The treatment was conservative with sulfanilamide medication, which was ap-

parently successful until an overwhelming acute pyelonephritis deranged the patient's resistance and brought about a fatal termination.

Tuberculosis and the Charcot type of degenerative and reparative lesion of the spine had to be excluded in the differential diagnosis. Infective agents other than the streptococcus which were considered were the *Bacillus typhosus*, *Bacillus melitensis*, *Staphylococcus albus* and the pneumococcus. Post-mortem smears showed a few degenerate-appearing streptococci, and post-mortem cultures from the abscess (retroperitoneal, along the spine) proved the validity of the assumption that the *Streptococcus beta haemolyticus* was the invading organism, and indicated that the treatment had been correct as far as medication was concerned. The outcome with surgery might have been better, however.—*R. S. Bromer.*

Geschickter, Charles F., and Maseritz, I. H. Skeletal metastasis in cancer. *J. Bone & Joint Surg.*, April, 1939, *21*, 314–322.

This article is based on a collection of 5,739 cases of carcinomata arising from various organs. Its purpose, the authors state, is to emphasize the incidence of skeletal metastasis in which there is no clinical evidence of a primary lesion, and to submit other data relative to osseous invasion by metastatic carcinoma. There were 356 cases in which carcinomata metastasized to bone. The primary source of the metastasis was definitely determined clinically in 296 instances. In 60 cases, or 16.8 per cent, however, there was no clinical evidence as to the source of the primary growth. The first indications of disease in this group of metastases of unknown origin were symptoms referable to the skeletal system. "Rheumatic pain" was a common complaint, and in several instances the patients were treated for arthritis. In 1 case a mass was palpated in the neck, and this later proved to be a lymph-node metastasis; in the remaining 59 cases there were no subjective or objective findings referable to other systems. Pathological fractures occurred in 19 instances, or 31.6 per cent, and solitary lesions in 34, or 56.6 per cent. The bones involved, in order of frequency, were: femur, spine, humerus, pelvis, ribs, skull and other bones to a lesser degree. The diagnosis in each instance was dependent on microscopic study of sections removed at biopsy. In sections with typical histological changes of hypernephroma, it was possible to determine the source of the metastatic lesion on the microscopic evidence. In the remaining cases a diagnosis of metastatic carcinoma could definitely be made from the sections, but no opinions were ventured as to the possible sources of the lesions.

The roentgenographic changes in metastatic carcinoma vary. The lesion is often solitary and may simulate many types of bone affections. It may present a localized area of osteoporosis and resemble the osteolytic variety of osteogenic sarcoma, or a patchy sclerosis and resemble the sclerotic type. Similarly, multiple lesions of carcinoma may simulate those of Hodgkin's disease, the leukemias, and multiple myeloma, making it impossible to differentiate the various affections roentgenologically. Ewing's sarcoma, chronic osteomyelitis, syphilis, tuberculosis, osteitis fibrosa cystica, and other tumors of bone may closely resemble lesions of carcinoma.

The prostate is the most common source of skeletal metastasis; the breast, second; the kidney, third, while the stomach, lung, thyroid and other organs are involved less frequently and in the order given. The size of the primary lesion is no index of the probability of metastasis. Metastatic involvement of bone may occur many years following the primary operation, and in the series reported in this article, breast cancer skeletal metastasis was observed as late as 18.25 years postoperatively. Irradiation of the osseous lesions relieves pain and prolongs the life of the patient.—*R. S. Bromer.*

Rankin, John O. Adamantinoma of the tibia. *J. Bone & Joint Surg.*, April, 1939, *21*, 425–432.

Adamantinoma is an epithelial tumor which arises from the enamel organ of the teeth and ordinarily occurs in either the maxilla or the mandible. There have been reported a comparatively large number of cases in this location. Occasional cases of the condition occurring in the region of the pituitary gland have been recorded. One case involving the ovary has been reported by Thoma. In the remaining reported cases the adamantinomata have occurred in the tibia. The author's case is the eleventh instance of its occurrence in the tibia reported in the general literature and the sixth to be found in the American literature.

The theories of the etiology of tibial adamantinomata are very intersting, but by no means proved at the present time. In general, two theories have been advanced. The first is that from early fetal life there has been a cell-rest in the tibia, which becomes activated in later life to form one of these tumors. The second is that, due to trauma or for some other reason, epithelium is implanted into the periosteum and later develops into adamantinomatous tissue.

Clinical and roentgenographic examinations are insufficient for establishing a diagnosis. Even on histological examination the diagnosis is not clear-cut, as is shown in the author's case and in other reported cases. Adamantinoma is a slow-growing tumor, which does not metastasize, but recurs unless completely removed. The time of recurrence varies from a few months to several years. Rankin believes that, if the growth is not too extensive, it can be removed completely at the first operation by radical saucerization and curettement. If a second operation is necessary, the operation which he describes in this paper is certainly superior to an amputation.

The roentgenographic appearance of the lesion in the tibia was an intramedullary, multilocular expanding tumor without any proliferation or thickening of the periosteum.—*R. S. Bromer.*

KLEINBERG, SAMUEL. Malignant giant-cell tumor of bone. *J. Bone & Joint Surg.*, April, 1939, *21*, 433-441.

Kleinberg states that it has been variously estimated that from 3.5 to 15 per cent of giant cell tumors of bone undergo malignant change. Sufficient evidence, he believes, has now accumulated in the literature to emphasize this unfortunate possibility. If a giant cell tumor is not treated and continues its natural development, as many did several generations ago before the opportunities for treatment were appreciated, it may spontaneously regress and disappear, but in the majority of cases it increases in size and the patient succumbs from hemorrhage or sepsis. In no instance of an untreated case is there a record of the appearance of malignancy or pulmonary metastasis. However, in recent years, few, if any, such tumors go untreated, and many are subjected to vigorous, repeated, and not infrequently often repeated treatments. The supervention of malignancy has been recorded only in such treated cases. It is admitted that the customary conservative methods of irradiation or surgery, alone or combined, are successful in the majority of cases, but Kleinberg thinks malignant transformation in the remainder should be prevented if possible.

A reasonably accurate diagnosis, without biopsy, can be made, based on the history, age of the patient, location of the lesion, and the roentgenographic appearance. These elements suffice in the majority of cases, but, because of the fact that they are variable, a positive diagnosis is not really possible without a biopsy. In the author's experience, he cannot recall a single instance of either a benign or a malignant tumor in which a simple, surgically well planned biopsy has caused any untoward symptoms, aggravation, or progression of the disease.

In his patient the lesion was located in the distal end of the tibia. From the history of the comparatively long course of the illness Kleinberg assumes that it was originally a benign giant cell tumor. It is difficult to speculate, he says, when malignancy set in. Although there was a history of injury subsequent to which the patient became acutely aware of the tibial lesion, yet for months previously he had frequently felt a twinge of pain in the leg. As the patient indulged in many athletic sports, perhaps he had injured the leg on many occasions and in that manner had stimulated the malignant change. It may be permissible to believe that the lesion may have had a low grade of malignancy originally, which was further attenuated but not entirely destroyed by intensive irradiation, and that subsequent minor traumata excited a full development of malignancy. Appreciating that many giant cell tumors of bone have been cured by irradiation, nevertheless Kleinberg feels that a more satisfactory procedure in his case, which was readily accessible to surgery, would have been thorough removal of the tumor tissue, supplemented by cauterization of the wound. This was advised by the surgeon, originally consulted by his patient. Knowing through abundant evidence, that a giant cell tumor of bone may become malignant and prove fatal, he is convinced that when a giant cell tumor can be treated surgically it should be completely excised at the earliest opportunity. Furthermore, in order that there shall be no doubt about the diagnosis, which cannot be diagnosed with certainty from the roentgenographic appearance alone,

a biopsy ought to be performed in every accessible lesion which may be a giant cell tumor. He believes irradiation should be reserved for giant cell tumors of inaccessible bones.—*R. S. Bromer.*

BLOOD AND LYMPH SYSTEM

Dimtza, A., and Jaeger, W. Arterielle Obliterationen der unteren Extremitäten bei der Arteriosklerose und bei der Endangitis obliterans. (Arterial obliterations of the lower extremities in arteriosclerosis and endangitis obliterans.) *Fortschr. a. d. Geb. d. Röntgenstrahlen*, July, 1939, *60*, 65–68.

These observations are based on 200 cases having "total arteriograms." The technique consists in the use of a film 20×90 cm. in size. which is exposed in two sections. The upper half nearer the site of injection is exposed first with the lower half covered, then when the contrast medium has reached the lower leg the procedure is reversed. Thorotrast is preferred to the organic iodine preparations and no injurious effects of its use have been observed. Arteriosclerotic vessels usually appear dilated and tortuous with irregularities of the inner wall which may contain calcium. The vessels of endangitis appear straight and narrow with smooth walls and spindle shaped constrictions. In Raynaud's gangrene there is no alteration of the large vessels. True obstruction due to disease of the vessel wall is recognized (1) when there is a sudden interruption of the vessel lumen, (2) when the interruption has a sharp border and shows no dilution of the medium and (3) when the interruption corresponds to evidence of a collateral circulation. The extent and size of the collateral circulation is an index of the duration of the obstruction. The number, form and extent of the obstructions are not characteristic but obstructions due to arteriosclerosis tend to occur in the lower femoral and popliteal arteries while those of endangitis obliterans are more common in the upper portion of the femoral artery. Surgical extirpation of the obstruction together with other conservative measures yields good results.—*W. A. Evans, Jr.*

ROENTGEN AND RADIUM THERAPY

Nitzge, K., and Iven, H. Über die Protrahierung der Röntgendosis. (Protraction of the roentgen dose.) *Strahlentherapie*, 1938, *62*, 91–108.

The question of dosage of roentgen rays has been studied for a long time on plants of various types. These authors also utilized plants for their studies which were carried out between 1934 and 1935. The plants were tobacco, tomatoes, soya beans, maize, dry seeds and germinated tissue. When the protracted dose was used it was found that for dry seeds there was obtained a simple summation of the dose according to the Bunsen-Roscoe law while for germinated tissue the Schwarzschild's law was found applicable. Most of the experiments were carried out on tobacco which was found especially suitable for this purpose, in consideration of the long observation periods of two to three months necessary when this method is employed.

In the irradiation of germinated tissue numerous constantly recurring, and therefore typical accompanying phenomena associated with a disturbance in growth were observed. In the maize experiments peculiar changes of the condition of the blossom and fruits as well as a splitting of the fruit bulbs were found. Some growth deviations were observed which could be produced also by other external factors such as manuring and heat or by internal factors such as bastardization.

In the tobacco largely employed for these experiments a series of anomalies were demonstrable depending on the degree of roentgen dosage. The germinal layers presented only slight changes. On the buds, however, even minute doses produced anomalies which, when followed up by irradiation with larger doses, developed into pronounced striking deformities. On the basis of the results obtained from a study of the protracted effect of roentgen rays on tobacco and other plants it may be stated that the results clearly show the significance of a further follow up study of the injuries resulting from the irradiation as contrasted with the injuries resulting from a single irradiation. This type of study is especially valuable for the determination of the protracted fractionated roentgen dose. It will be desirable to carry out similar experiments on other types of plants, but even these limited experiments are of great significance for daily practice where roentgen irradiation is used.—*A. S. Schwartzman.*

Jovin, I. Die Behandlung des metastatischen Krebses der Halslymphdrüsen. (Treatment of metastatic carcinoma of the cervical lymph glands.) *Strahlentherapie*, 1938, *62*, 262–286.

1. Not all palpable glands are carcinomatous; on the other hand, a metastasis may remain non-palpable for a long time. The clinical examination therefore permits a recognition of the true character of the glands only in a small percentage of the cases; in consideration of the above, one must assume the existence of a metastasis and the cervical region should be treated even where there are no palpable glands.

2. The necessary prophylactic treatment of Group I must be recognized. The methods employed vary. Surgeons recommend an extensive operation; radiologists, on the other hand, do not favor this disfiguring operation and such pathologists as Ewing support this view. Jovin varies his procedure from case to case depending on the type of primary tumor, on the general condition of the patient, on the cure of the primary tumor, etc. This method of procedure, however, requires great clinical experience.

3. The method of treatment of cases belonging to Group II varies in the different institutions. Quick, Bervin and other American authors recommend postoperative irradiation; Simons and Fischel do not advise postoperative irradiation. At present most authors use the surgical method of treatment of glandular metastasis preceded by radiation treatment. The operation must be carried out under the rules of cellular asepsis; it must be sufficiently extensive in order to permit the removal of the muscles, aponeurosis, vessels and glands "en bloc." Jovin is of the opinion that the postoperative irradiation is very useful and should be systematically employed.

4. Most authors agree as to the method of treatment of carcinoma of Group III. In these cases the operation is useless and actually dangerous. The chance of a successful postoperative irradiation following an incomplete operation is minimal. Only exceptionally is it possible to decrease inoperable glands by irradiation and render them operable. In cases of this type radiation therapy alone must be resorted to as a palliative measure. The following principles are recommended by this author for the treatment of glandular metastasis in the region of the neck:

Group I. Observation, external radium or roentgen therapy, operation, operation and irradiation, depending on the given case.

Group II. Operation. In border line cases of operability, irradiation before the operation and then operation. External radium or roentgen therapy for technically operable cases but where the operation cannot be carried out because of poor general condition. Postoperative irradiation in each case.

Group III. Radium or roentgen therapy.—*A. S. Schwartzman.*

GAJZAGO, E. Die Bedeutung der Röntgenschwachbestrahlung in der Gynäkologie. (The significance of weak roentgen radiation in gynecology.) *Strahlentherapie*, 1938, *62*, 167–173.

In gynecology there are three indications for the inflammation inhibiting roentgen irradiation: mastitis, thrombosis and adnexitis. Of these three diseases best results are obtained from the roentgen radiation in the treatment of mastitis. The significance of these favorable results is accentuated by the fact that mastitis is a very frequent affection. It is generally known that the sensitiveness of the functional mammary gland towards pyogenic organisms is increased especially since a milk congestion alone is sufficient for the production of an affection. The danger is increased as a result of the fact that during breast feeding the nipples may not be properly cared for; cracks develop which serve as a portal of entry for the pyogenic organisms; because of the above, mastitis is a very frequent disease.

Roentgen irradiation of mastitis was employed for the first time about fifteen years ago Heidenhain and Fried were the first to mention the roentgen treatment of inflammatory diseases at the German Surgical Congress in 1924. Since then the subject has been extensively studied by many authors. In the course of the last seven years this author carried out 150 irradiations of the mammary gland. The dose used per radiation field of 8×10 cm. up to 15×15 cm. square, was 50 to 150 r, individualized according to the depth of the disease focus. This dosage would come under the designation of "weak" radiation.

Even though the nature of the effect of these rays is not clearly known, nevertheless in most of the cases treated a curative effect was obtained. As yet no satisfactory explanation can be offered in regard to the mechanism of action. Under the influence of the roentgen irradiation there occurs an immediate or very prompt disappearance of pain. Together with the above there occurs an improvement of the general

condition, a fall of temperature and a rapid cure. In some cases there occurs a temperature elevation following the irradiation but this is of short duration. In a third group of cases the curative effect of the irradiation is not as striking as in the first two groups and the temperature falls by lysis while the local and general symptoms decrease and eventually disappear in the course of a few days.

The author also employed this type of radiation in the treatment of 60 cases of thrombophlebitis. In not a single case did an embolism occur. The results obtained in these cases were very satisfactory and better than those obtained by any other method of treatment hitherto employed by the author.—*A. S. Schwartzman.*

Hamann, A., and Göbel, A. Sechsjahresergebnisse bei der Behandlung der Gebärmutterkrebse im Allgemeinen Krankenhaus St. Georg zu Hamburg. (Results of the treatment of carcinoma of the uterus in the course of six years in the General Hospital of St. George of Hamburg.) *Strahlentherapie*, 1938, *62*, 251–261.

In a previous communication these authors reported the results obtained by them from the treatment of carcinoma of the uterus where the patients were under observation from two to four and one-half years. The present report is based on a followup observation of the same cases up to six to eight and one-half years. The present report is based on a study of the pure radiation effect on carcinoma of the cervix. Some studies were carried out also regarding the effect of roentgen radiation on carcinoma of the body of the uterus and these results are compared with those obtained from purely surgical and surgical-radiation treatment of carcinoma of the cervix and of the body of the uterus.

Carcinoma of the Cervix. On December 31, 1933, of the 203 patients with carcinoma of the cervix treated by irradiation alone, 51 remained alive and free of symptoms. On December 31, 1937, 37 of these were alive and free of symptoms, 5 were free of symptoms but died from intercurrent disease four years after the treatment and 9 died from carcinoma.

Most deaths occurred during the first one and a half years after treatment was instituted. After one year only about 54 per cent of the patients remained alive, after one and a half years only 40 per cent remained alive. During the following one and a half years, that is at the end of the third year, only about 27 per cent remained alive and during the following three years, that is at the end of the sixth year of treatment, only 20 per cent remained alive. Of the 203 cases treated, 44, or 21.7 per cent, lived longer than five years and 41, or 20 per cent, lived at least six years. A study of the cases in regard to the stages of carcinoma at which treatment was instituted showed that 40.7 per cent of those remaining alive after six years and free of symptoms were those who came to treatment while in Stage I.

No essential difference was found in regard to the age of the patients. The results, however, were somewhat better in younger than in middle-aged women. Below sixty years of age the earlier results were definitely more favorable. After six years of observation 22 per cent of those remaining alive were between twenty-one and forty years of age, 17 per cent were between forty-one and sixty years of age and 20 per cent above sixty-one years. If we further consider the mortality resulting from intercurrent infections the results in the last mentioned group appear even more favorable.

Carcinoma of the Body of the Uterus. Of the 13 patients with carcinoma of the body of the uterus of Stages I to IV, 4 were alive and free of symptoms on December 31, 1933. Two of these remained free of tumors. In 2, recurrences appeared during the sixth year, in one in the lesser pelvis and in the other in the vulva and in the inguinal regions. The last mentioned 2 patients were still alive seven years after the treatment of the primary tumor.

Recurrences. Of 35 cases of surgical recurrences, 33 cases of carcinoma of the pelvis and 2 cases of carcinoma of the body of the uterus, 7 remained alive on December 31, 1933, 2 of which were the two women with carcinoma of the body of the uterus. These 2 patients remained alive and free of symptoms on December 31, 1937. Of the remaining 5 cases 2 died, one from intercurrent infections and the other from another recurrence.

Results obtained from the surgical and radiation treatment of carcinoma of the uterus:

1. *Carcinoma of the Cervix.* Of 58 operative cases 46 of which were later treated with roentgen rays, 27 remained free of symptoms on December 31, 1933. Since then 3 cases died, 1 from pulmonary tuberculosis during the sixth year after the operation and 2 from carcinoma

three and six years after the operation respectively; 26 of the 58 cases remained alive and free of symptoms five years after the operation and 24 of the 58 remained alive and free of symptoms six years after the operation.

Of the 20 cases operated on at another clinic but treated in the present clinic by roentgen irradiation, 8 remained free of symptoms on December 31, 1937. The results obtained from the combined surgical and radiation treatment were: Free of symptoms and alive 42.4 per cent after five years and 39.8 per cent after six years following surgery and roentgen treatment.

2. *Carcinoma of the Body of the Uterus.* Fifty per cent of the 14 cases treated remained alive and free of symptoms five and six years after the operation. One patient died from carcinoma two years after the operation.—*A. S. Schwartzman.*

MISCELLANEOUS

STAUNIG, K., and LÖBERING, J. Über einen neuen Röntgeneffekt. (A new roentgen effect.) *Strahlentherapie*, 1938, *62*, 73–90.

Roentgen rays have a definite effect on the atomic structure of tissue. It is conceivable that this effect is not limited to the atom alone. In consideration of the above the authors studied the effect of roentgen rays on the swelling ability of various tissues; they have found that this ability to swell undergoes a change when the tissue has previously been acted on by roentgen rays. Depending on the tissue used, it was found that under the influence of roentgen irradiation the degree of swelling is either increased or decreased. In the experiments carried out hitherto it was found that in many instances the ability of the tissue to swell increased following the irradiation by 3.6 per cent above normal while in other cases the same ability was decreased by 1.4 or more per cent. The structure of the tissue apparently influences this change considerably. Changes in the swelling ability were observed in bone marrow, cartilage, lung tissue, testicular tissue, ovarian tissue, striated muscle, thyroid tissue and pancreas. Extensive studies have shown that the presence of the biological cell is unnecessary for the appearance of the above mentioned changes and that the effect appears in the absence of biological cells in a similar manner. Apparently other properties of the substance which must be looked for in the chemico-physical structure are responsible for the changes resulting under the influence of roentgen irradiation. It was found, for instance, that the same changes in the swelling ability occur in gelatin as in cartilage and in numerous other animal tissues. These findings would indicate that in the evaluation of the roentgen effect the molecule of the tissue irradiated is of significance. Under certain conditions the molecule is capable of changes when the roentgen rays are acting on it. The changes in the molecule come to manifestation in the form of changes in its external valences. The biological effect of roentgen rays is basically the result of the fact that the vital manifestations are dependent on changes taking place in the colloidal condition. These data are of great value for roentgen therapy.—*A. S. Schwartzman.*

LASZLO, D., and FLEISCHMANN, W. Strahlenwirkung auf den Zellstoffwechsel. (Effect of radiation on the cellular metabolism.) *Strahlentherapie*, 1938, *62*, 151–155.

Many problems pertaining to the biological effect of radiation still remain unclear. One of these problems is the latent time. If, for instance, a cellular culture is irradiated with 120 mg-hr. of radium, this dose does not suppress the cellular growth immediately. According to the computation of Lischer, about 15 g. of radium is necessary in order to produce an immediate cessation of growth and an immediate cellular death. The duration of the latent time is constant with constant radiation doses and is independent of the proliferation size of the cell. With increasing radiation intensity the duration of the latent time is shortened. Canti and Spear have found that the mitoses disappear rapidly after irradiation with small doses. According to Fischer the cessation in growth following the irradiation can not be explained by the fact that only the cells in a state of mitosis are affected by the rays. If this were correct one could expect an immediate effect of the irradiation. His experiments may be interpreted only in the sense that all cells are uniformly affected by the rays. He is of the opinion that the irradiated cells liberate growth inhibiting substances which gradually lead to a cessation of growth of the culture. Heeren studied extensively the latent time of the radiation effect and expressed the opinion that the time interval of the latent period will be considerably shortened with a further improvement of our methods of study. The question arises whether the inhibition of growth is the result of an inhibition of the energy metabo-

lism of the cells or whether it is the result of a change, for instance, of the colloidal makeup or other physical factors of the cells.

Another important problem is the extent of the dependence of the cellular metabolism or cellular growth resulting from the radiation effect on the dosage employed. Andersen and Fischer studied the influence of alpha rays on the rate of growth of tissue cultures; they found an inhibition but no acceleration even when minutest doses were used. The stimulation theory of small doses has been substantiated by some findings and negated by others.

Another important problem is the reversibility of the changes resulting from the irradiation. Canti and Spear found that the mitotic figures which disappear following the irradiation with a slight dosage reappear and are even more numerous when the irradiation has ceased. More or less similar findings were made by Laser. Heeren found that slowly growing roots are inhibited by the irradiation but their growth is transitorily accelerated after the irradiation has ceased. The same author found that the respiration of liver tissue decreases during the irradiation but returns to normal later.

An attempt was made by these authors to study experimentally the problems of the latent period promotion and inhibition as well as reversibility of cells under the influence of irradiation. A series of suspensions of nucleated red blood corpuscles in sugar containing isotonic salt solution were prepared and the respiration of these cell suspensions was measured by means of Warburg's apparatus. In the same experiments the sugar containing salt solution was charged with a radium emanation of a certain concentration. In a series consisting of 22 experiments it was found that the oxygen utilization without the emanation during the first hour was equal on the average to 161 $mm.^3$ and with the emanation it was equal to 122 $mm.^3$; therefore, it was about 25 per cent less. In not a single experiment was there an acceleration of the oxygen consumption or an increase observed.

On the basis of the findings made by these authors it may be stated that in experiments approximating as closely as possible to physiological conditions the cellular respiration is definitely inhibited by radium emanation, is never accelerated, and the inhibition is reversible in that it disappears after the emanation has been removed. The inhibition and normalization of respiration following removal of the emanation are practically without latency. These findings may be interpreted as a probable influence on the respiratory ferments by the radium in the presence of an intact cellular structure.—*A. S. Schwartzman.*

Holthusen, H. Die allgemein-biologische Wirkung der Röntgenstrahlen. (The general biological effect of roentgen rays.) *Strahlentherapie*, 1938, *62*, 228–239.

Definite conceptions regarding the effect of roentgen rays on living tissue have developed parallel with the development of roentgen therapy. It is generally assumed at present that basically the effect of roentgen rays consists in a direct or indirect sequel of energy changes which occur in the cell following the radiation absorption. For purposes of generalization the process at the basis of the biological roentgen-ray effect may be designated as "radiochemical process." It has been shown that the effect depends on the amount of the absorbed radiation. Following a therapeutic roentgen irradiation even with larger doses the absorbed energy units are so small that it cannot be measured by the available quantitative chemical analytic methods. Studies of the radiosensitiveness of ferments and of vitamins have more or less shown clearly that the biological radiation effect is not dependent on an influence of these substances. Where chemically quantitatively demonstrable changes in the makeup of a biological substance do occur following a roentgen irradiation, the roentgen irradiation is usually carried out with very large doses hardly ever used therapeutically.

The roentgen effect on the living cell can be based only on such processes which are capable of influencing the independent processes of cellular life, especially if one deals with biologically different substances, and this influence is achieved by a very slight amount of roentgen radiation. Apparently the origin of biologically highly different substances determines the sequel of roentgen irradiations and is responsible for the phenomena generally designated as "general effects" of roentgen rays.

The indications of roentgen therapy, insofar as one does not deal with destruction of pathologic tissue, are practically the same as those for protein body therapy. It is conceivable that analogous substances are effective in both cases in each of which a very small amount of sub-

stance is necessary in order to produce the effect. Such reasoning indicates that the roentgen rays act basically on the protein molecules.

It has been observed that the sequelae of roentgen irradiation are manifested after a variable length of time or after a variable interval. The process of roentgen irradiation and its later manifestation has been justly compared by some authors with the process of the exposure and later development of a photographic film; in both cases the effect of the irradiation is not demonstrable immediately but only after a certain length of time.

Muller has shown that the sequelae of irradiation may be manifested only late in the course of the development of the individual resulting from the irradiated germinal cell. It has been more or less definitely proved at present that the number of mutations following the irradiation of the germinal cell is proportional to the dose of roentgen rays. There is basis for the assumption that even when a single electron charge passes close to a sensitive gene, this gene ceases to function and there appear all symptoms resulting from this lack of function. With an increase in the dose the number of occurrences of this type is bound to increase and consequently also the frequency of mutations. The type of changes appearing, however, and the presence of a visible or a latent mutation and the relation of these to each other are independent of the roentgen-ray dosage. Under the influence of irradiation of growing embryos and proliferating tissue processes, changes appear which may be designated as somatic mutations. These somatic mutations are manifested in the form of changes of shape of the leaves of the growing tree or changes in the rate of growth. When growing embryos are irradiated by roentgen rays and if small doses are used, malformations appear during the later development even though the embryo developed normally originally. When larger doses are used disturbances in development may appear earlier but after a certain interval of time.

On the basis of the available data one is justified in stating that a time relationship in the appearance of later radiation degenerations suggest an injury of the gene resulting from degeneration. The somatic injuries present a more or less definitely pronounced time factor. It is conceivable that on repeated irradiations there occurs a summation of the radiation effect in the chromatin substance.—*A. S. Schwartzman.*

WILKINSON, F. R. Rapid roentgenography in the operating room, with a single solution. *J. Bone & Joint Surg.*, 1939, *21*, 387–392.

Roentgenographic control of operations upon bones is coming into more general use. Its field of greatest usefulness, perhaps, is found in operations upon the hip, notably for fracture of the neck of the femur, in which a Smith-Petersen nail is introduced by the so-called "blind method." All the numerous methods of blind nailing depend, to a greater or lesser degree, upon roentgenographic control. Several roentgenograms must be taken during the course of the operation. Many of the patients are elderly and are poor operative risks. Anything which decreases the time which they spend on the operating table under anesthesia is of definite value.

Wilkinson had been using a developer heated to 100° F. The film was overexposed, placed in this developer for approximately thirty seconds washed in water, placed in "hypo" for about one and one-half to two minutes, washed again and was then brought to the operating room. This he found had disadvantages:

1. Without thermostatic control it was impossible to keep the developer at a constant temperature, and a variation of even a few degrees made a marked difference. If the developer was too cold, the film was underdeveloped; if too hot, the film was overdeveloped or the emulsion melted and ran.

2. It was not possible to develop and fix the films in less than three minutes.

3. Three containers, for developer, water and "hypo," were required.

4. It was essential to have the dark room close to the operating room unless more valuable time was to be lost.

In Wilkinson's search for a simpler method for the rapid development and fixation of a roentgenogram he found an article by Ollerenshaw,* who evolved a single solution with which adequate films are developed and fixed in one minute. After experimentation, using modifications of the formula recommended, Wilkinson developed a formula which he gives in detail with instructions for mixing and its use. He finds it is faster and simpler in that only one solution is required. Its use has eliminated the poor results occasioned by variation in temperature of the hot developer. The solution is used at room temperature.—*R. S. Bromer.*